RENAL CLEARANCE OF SODIUM COLISTIN METHANESULFONATE IN NORMALS AND PATIENTS WITH RENAL DISEASES

"A guide for the dose schedule in patients with impaired renal function"

TAKESHI SHIRAI, MASAYUKI TAKASUGI, AKIHIKO KITAMURA,
HIROAKI MINODA and HAJIME YAMAGA
Third Department of Internal Medicine, Faculty of Medicine,
Kyushu University, Fukuoka, Japan

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A recent increase in the incidence of infection due to gram-negative bacteria has drawn concern to the clinician as therapeutic problems. Accordingly, a number of antibiotics effective to gram-negative bacteria has been developed. Sodium colistin methanesulfonate (MCM) is the sodium salt of the methane sulfonate derivative of colistin, which is effective to gram-negative bacteria, and is also known to be effective to the bacteria which have been insensitive to commonly used antibiotics. Some physicians, however, tend to avoid administration of MCM to the patients with chronic urinary tract infection accompanied by chronic renal functional impairment or gram-negative infectious diseases complicated by renal disease even when causative bacteria of the infection are sensitive to the MCM and relatively resistant to commonly used other antibiotics. This is because they feel that MCM might have strong nephrotoxic potency since polymyxin B is known to cause impairment of renal function (MCM belongs to polymyxin group, and is polymyxin E). Actually, MCM itself has little nephrotoxic potency as compared with polymyxin B, but high serum levels of MCM is likely to occur in patients with renal insufficiency, because MCM is eliminated mainly by renal excretion. This very high serum levels of MCM may give rise to unpleasant side effects. Therefore, toavoid over administration of MCM in patients with renal functional impairment, the dose schecule should be adjusted according to their renal function. Thus renal clearance of MCM and other renal function tests including creatinine clearance and PSP excretion test have been measured in the normal subjects and patients with renal diseases with or without renal functional impairment, and adequate administration plan for the patientrs withrenal functional impairment have been established.

MATERIALS AND METHODS

Twenty cases of chronic renal diseases of varying etiology (including chronic glomerulonephritis and chronic pyelonephritis), and 10 cases of healthy volunteers were used in this study. The age range of the group of renal diseases was 15 to 66 years old, and those of normal subjects was 23 to 39 years old.

A dose of 66.8 mg base potency (2,000,000 units) of MCM was injected intramuscularly and blood samples and urine specimens were collected according to the clearance schedule, *i.e.* before injection of MCM and 30. 60 and 90 minutes after the injection. At the same time paraaminohippuric acid (PAH) clearance was measured by single intravenous injection of PAH. The load of PAH was adjusted according to the result of previously performed PSP excretion test. Also 24 hours endogenous creatinine clearance was determined on the next day.

The concentration of MCM was determined by the method of bioassay using NIH J strain of *E. coli*.

RESULTS

I) Serum and urine concentration of MCM following single intramuscular injection of 66.8 mg base potency (2,000,000 units) of MCM.

i) Serum levels of MCM (Fig. 1).

As shown in Fig. 1, the average serum levels of MCM in normal subjects rose slowly to 2.5 μg/ml after 30 minutes, 2.7 μg/ml after 60 minutes, and 2.9 μg/ml after 90 minutes of injection. In the group of the patients with chronic renal diseases without renal functional impairment (more than 25 % of PSP excretion in 15 minutes), the average serum level reached to 4.6 μg/ml after 30 minutes,

Fig. 1 Serum levels of MCM after 66.8 mg of MCM I.M. Injection.

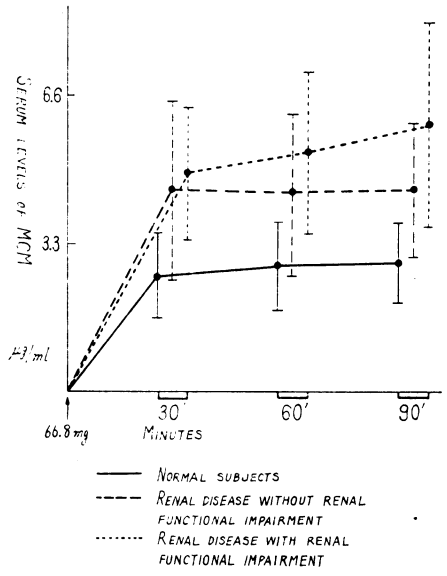
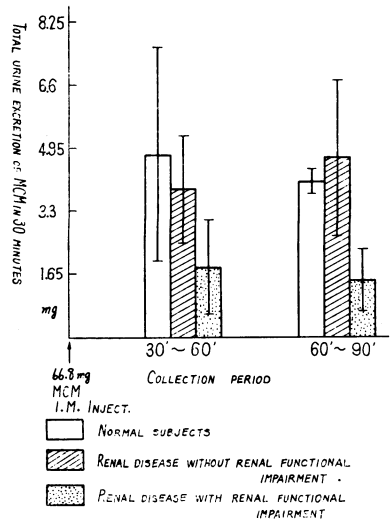


Fig. 2 Total urinary excretion of MCM



and thereafter the serum levels of MCM maintained about the same levels. In the group of the patients with renal functional impairment (less than 24% of PSP excretion in 15 minutes), the average serum level of MCM rose to 4.9 μg/ml after 30 minutes, 5.1 μg/ml after 60 minutes, and 6.3 μg/ml after 90 minutes.

ii) Urine excretion of MCM (Fig. 2)

In the group of the normal subjects, the average total excretion of MCM was 4.5 mg at the period of the first 30 to 60 minutes, and 3.7 mg at the period

Fig. 3 Serum levels and urinary excretion of MCM in a patient (GFR: 47 ml/min) following intramuscular injection of 66.8 mg and 133.6 mg of MCM in two separate occasions

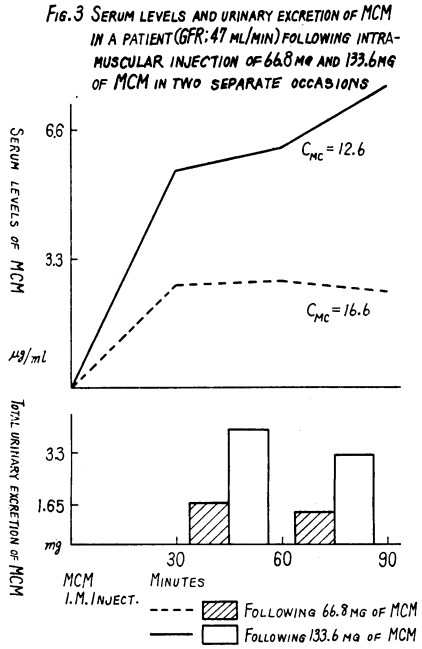


Table 1 C_{MC}, $C_{Creat.}$, C_{PAH} and PSP excretion in 15 minutes in the normal subjects and patients with renal diseases.

	Normal subjects		Patients with renal diseases	
	average	range	average	range
C_{MC} ml/min.	47.5	35.7~63.5	20.9	2.0~59.6
$C_{Creat.}$ ml/min.	77.9	60.1~102	45.4	3.8~77.9
C_{PAH} ml/min.	535.4	331~713.8	306.1	11.5~593
PSP % 15 min.			20.9	1.0~52.7

of 60 to 90 minutes. In the group of the renal diseases without renal functional impairment, the average total excretion of MCM was 4.1 mg in the first 30 minutes collection period and 4.5 mg in the next 30 minutes collection period. The urine MCM in the group of renal diseases with renal functional impairment was 1.8 mg in the first 30 minutes and 1.5 mg in the second 30 minutes collection period.

A patient with moderate renal functional impairment (GFR : 47 ml/min.) was injected two doses of 66.8 mg base potency (2,000,000 units) and 133.6 mg base potency (4,000,000 units) of MCM into the muscle on the separate days, and the serum levels of MCM and urine concentration of MCM were determined. As shown in Fig. 3, the larger dose gave

higher serum levels and excreted more in the urine. However, the values of clearance of MCM were almost the same at those two different serum levels (C_{MC} : 12.6 ml/min., and 16.6 ml/min.).

II) Clearance of MCM (C_{MC}), endogenous creatinine clearance ($C_{Creat.}$), PAH clearance (C_{PAH}), and PSP excretion test.

The average and the range of each clearance value were shown in Table 1.

III) Relationship between C_{CM} and other renal functions.

The C_{CM} and $C_{Creat.}$ (Fig. 4) : There was a good correlation between C_{CM} and $C_{Creat.}$ in the normal subjects and patients with renaldi seases, and their correlation coefficient "r" was 0.82. The C_{MC} and C_{PAH} (Fig. 5) : There was a good correlation between C_{MC} and C_{PAH}, although their correlation coefficient was not good as the former one. PSP excretion in 15 minutes and C_{MC} (Fig. 6) : There was a good correlation between those two in the patients with renal diseases, the "r" being 0.91.

DISCUSSION

As mentioned at the introduction of this article, the incidence of systemic infection due to gram-negative bacteria has been increasing, and the therapy of those infection has become serious problem, because many of those gram-negative bacteria are relatively insensitive to commonly used antibiotics. Thus, antibiotics with a high degree of activity against these gram-negative bacteria have grown to great importance.

Sodium colistin methanesulfonate is a basic polypeptide antibiotics found by KOYAMA[1], and is an effective bacteriocidal agent for the gram-negative bacteria which have been resistant to commonly used antibiotics, and the clinical effectiveness of this drug has been well established[2,3,4]. There is, however, some problems for the use of this effective drug to the patients with renal diseases with renal functional impairment ; (i) this drug is eliminated mainly by renal excretion, and administration of MCM in excess of renal disposal capacity may lead to high serum concentration of MCM and may cause

FIG. 4 RELATIONSHIP BETWEEN C_{MC} AND $C_{CREAT.}$

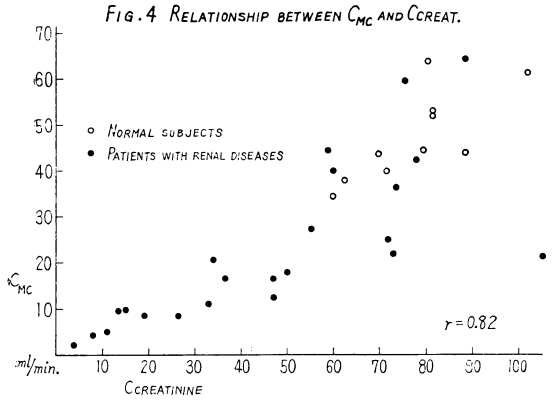


FIG. 5 RELATIONSHIP BETWEEN C_{MC} AND C_{PAH}

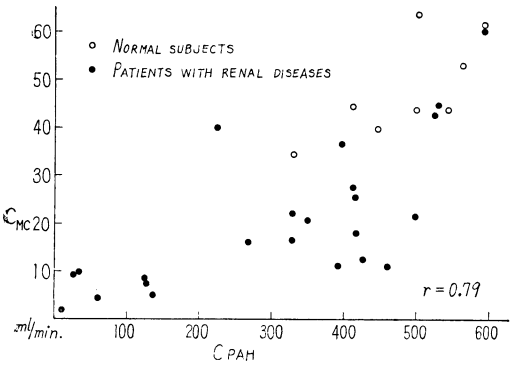


FIG. 6 RELATIONSHIP BETWEEN C_{MC} AND PSP EXCRETION RATE IN THE PATIENT WITH RENAL DISEASES

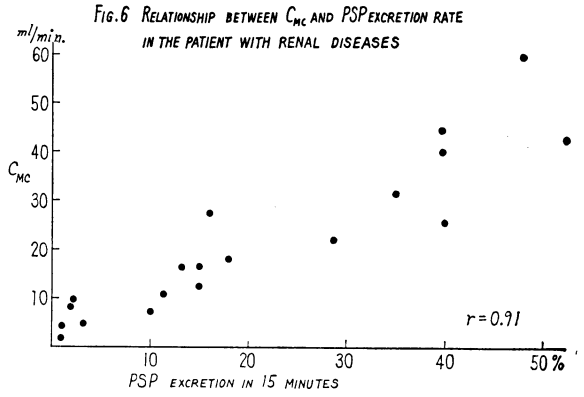
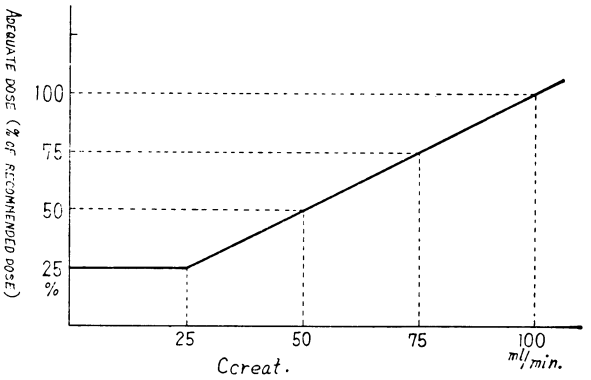


FIG. 7 ADMINISTRATING PLAN OF MCM ACCORDING TO $C_{CREAT.}$



many unpleasant side effects such as neurophychic disturbances, paresthesias and further deterioration of pre-existing renal disease, (ii) all the polymyxins are potentially nephrotoxic to the epithelium of convouluted tubules, although MCM (polymyxin E) has not so strong nephrotoxicity as polymyxin B. Concerning to nephrotoxicity to the human kidney, FEKETY *et al.*[3] studied nephrotoxicity of this drug by means of renal biopsy and concluded that they could not find any histological evidence of the nephrotoxicity of colistin. Also TALLGERN *et al.*[5] reported their experience of colistin treatment for a total 25 patients with impaired renal function of varying etiology, and stated that the histological finding did not differ from the expected underlying renal diseases, although transient deterioration of renal function occurred in some cases of their 25 patients with renal diseases with chronic renal failure. On the other hand, ELWOOD and his co-workers[6] observed that BUN were rised and acute ologuric fata renal failure developed in an advanced aged subject in the colistin treatment. But this may be resulted from abnormal serum concentration of MCM and this high serum levels of MCM might have caused further deterioration of the pre-existent minimal degree of renal changes.

Thus, to avoid high serum concentration of MCM seems to be the most important point of using of this drug, namely dosage should be reduced in proportion to the extent of the impairment of renal function. Concerning to this dosage reduction in patients with renal failure, GOODWIN *et al.*[7] studied 39 subjects with varying degree of renal function and decided recommended dosage plan according to the endogenous creatinine clearance. That is, i) when endogenous creatinine clearance exceeds 20 ml/min., 75 to 100% of the recommended daily dose divided into doses every 22 hr, (ii) when endogenous creatinine clearance is between 5 and 20 ml/min., 50% of the usual daily dose divided into doses every 12 hr., (iii) when endogenous creatinine clearance is lses than 5 ml/min., 30 to 35% of the normally recommended dose divided into doses every 12 to 18 hr. And this dosage plan seems to be excellent one, however, dosage plan appears to be relatively rough.

From our observation, there is a positive correlation between serum concentration of MCM and total urine excretion of MCM, and also there is a good correlation between C_{MC} and other renal function tests, although accurate mechanism of elimination of this drug from the kidney is not clear.

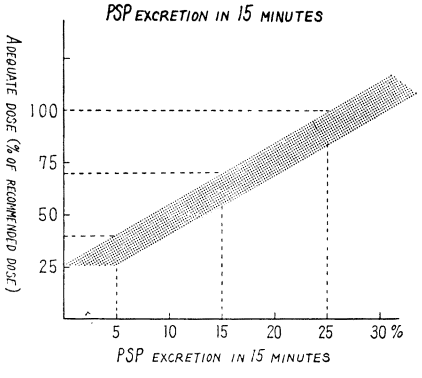
From our data MCM is mostly eliminated through the kidney and their clearance is about 50 to 60% of creatinine clearance (GFR). Thu sestimation of the critical administrating dose can be made depending upon the result of the creatinine clearance of GFR. Following formula can be used for the estimation of adequate dose in patients with renal failure.

$$\frac{\text{Creatinine clearance or GFR of the patient}}{100} \times \text{recommended daily dose (66.8 to 133.6 mg)} = \text{adequate daily dose for the patient with renal failure (\%)}$$ (Fig. 7).

For example, when creatinine clearance or GFR is 100 ml/min., daily adequate dose to this patient is 100% of recommended dose divided in two doses every 12 hours, aud when creatinine clearance is 75 ml/min., daily adequate dose of this patient is 75% of recommended dose divided in two doses every 12 hours and when the creatinine clearance is 50 ml/min., daily adequate dose is 50% of recommended dose divided in two doses every 12 hours. When creatinine clearance is 25 ml/min., the adequate dose is 25% of recommended dose. When the creatinine clearance is less than 25 ml/min., the dose should be adjusted by the period of the administration of this drug. It is important to note that minimum dose of MCM is necessary to maintain the effective body fluid concentration of MCM in patients with severe renal functional impairment.

When creatinine clearance and other glomerular filtration studies are not possible to perform, administrating dose may be adjusted by 15 minutes PSP excretion rate instead of creatinine clearance, as shown in Fig. 8. For example, when the results

FIG. 8 ADMINISTRATING PLAN OF MCM ACCORDING TO PSP EXCRETION IN 15 MINUTES



of PSP excretion in 15 minutes is more than 25%, 100% of the recommended dose should be given divided into two a day, when PSP is 15%, 75% of recommended dose is adequate dose of the patient ……and so on.

These admininstrating plan from our data essentially concurs with GOODWIN's claim, but our administration plan is more critical, and also more universal than their plan. When using this method in the sodium colistin methanesulfonate treatment to the patients with gram-negative infection complicated by renal disorder, unpleasant side effects of this drug will be avoided and successful treatment will be achieved.

CONCLUSION

To establish adequate administrating dose of sodium colistin methanesulfonate (MCM) in patients with impaired renal function, MCM clearance was measured with other renal function tests in healthy volunteers and patients with renal diseases. MCM clearance was about 50 to 60% of creatinine clearance and there was a good correlation between MCM clearance and PSP excretion rate of 15 minutes. Thus, adequate administrating dose may be adjusted by PSP test, and a dosage schedule according to creatinine clearance or PSP excretion test was introduced.

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