[Chem. Pharm. Bull. 22(6)1261—1264(1974)]

UDC 547.544.09 : 615.31.015

Methanesulfonic Acid Derivative of *p,p'*-Diaminodiphenylsulfone. II.[1] Pharmacokinetics and Availability of Parental Drug in Rabbit[2]

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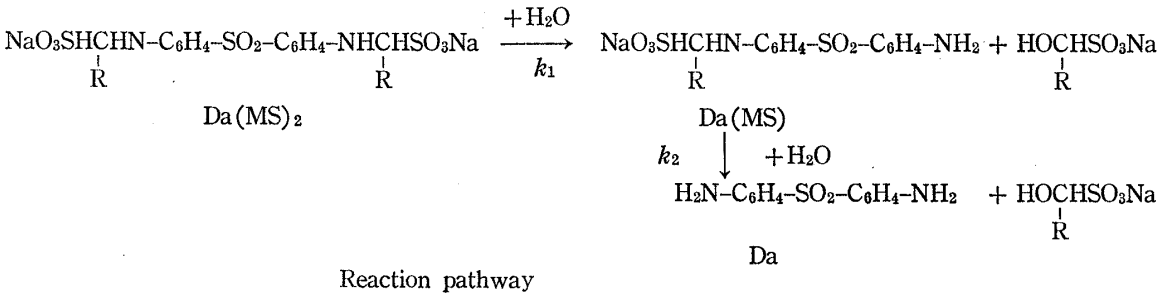
(Received August 9, 1973)

Pharmacokinetic studies on various methanesulfonic acid derivatives of *p,p'*-diaminodiphenylsulfone (Da) were carried out on rabbit and the liberation of parental Da was pursued. The general formula of the studied derivatives is $NaO_3SHCHN-C_6H_4-SO_2-C_6H_4-NHCHSO_3Na$, where R are H–, CH_3–, $HOCH_2(CHOH)_4$–(promin) and C_6H_5–. The time courses of the blood concentration for all the derivatives and parental Da administered intravenously were represented in biexponential equations. The elimination rates of the water-soluble derivatives were about 10-fold larger than that of parental Da. The distribution volume of central compartment for Da was larger than those of the derivatives. No detectable amount of Da was found in blood after the *i.v.* administrations of promin and the derivative of R=H. From the viewpoint of drug availability, the area under liberated Da *vs.* time curve was compared to that of intact Da and deconvolution calculation was also carried out.

In the previous study,[1] various methanesulfonic acid derivatives (MSD) of *p,p'*-diaminodiphenylsulfone (Da) have been synthesized and the *in vitro* release of parental Da from these derivatives was investigated kinetically which is represented as follows.



Reaction pathway

From the kinetic data on the hydrolysis of the methanesulfonic group, the induction period and the accumulation rate of free Da was estimated and it was anticipated that the availability of parental Da from some derivatives including promin may be negligibly small.

Present study is on the pharmacokinetics of these derivatives in rabbit and the amount of intact Da released in biophase from MSD administered was pursued. It may be a rational supposition that the bactericidal activity of the derivatives is expected only after the liberation of intact Da. For the evaluation of the availability of the parental Da from these water soluble derivatives, the comparison of areas under the Da blood level *versus* time curve and deconvolution method were used.

The abbreviations of the derivatives were represented by $Da(HS)_2$, $Da(MeS)_2$, $Da(GlS)_2$ and $Da(PhS)_2$ for the derivatives substituted by –H, $-CH_3$, $-(CHOH)_4CH_2OH$ and $-C_6H_5$ for R in the reaction pathway shown above.

1) Part I: K. Ikeda and Y. Kurono, *Chem. Pharm. Bull.* (Tokyo), **21**, 1198 (1973). This report constitutes Part V of the studies entitled "Methanesulfonic Acid Derivative of Drug."
2) Presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1973.
3) Location: *Tanabe-dori, Mizuhoku, Nagoya.*

Experimental

Biopharmaceutical Procedure——Methanesulfonic acid derivatives of Da were same to those used in the previous study.[1] Test animals were male rabbit weighing 2 to 3 kg. About 3.0×10^{-4} mole of each drug per 1 kg body weight was injected intravenously. The solution of $Da(MS)_2$ in sterilized distilled water which was passed through ion exchange column to expell the hydrolysis products was injected through ear vein. The *i.v.* injection of parental Da was made with propylene glycol as vehicle because of its low aqueous solubility. Blood sample (1.0 or 2.0 ml) was taken directly from heart with syringe and the analysis was carried out as follows.

Analysis of Blood Sample——The separative determinations of Da, Da(MS) and $Da(MS)_2$ are essentially same as in the previous studies.[1,4] In a test tube containing 10 ml of 0.1% saponin, 2 ml sample was taken for hemolysis. Two aliquotes of 4 ml saponified blood were subjected for determinations of $Da(MS)_2$ and Da respectively. Three ml of remaining saponified sample was submitted to the determination of total drug concentration.

Result and Discussion

Blood Levels of Various Da MSDs and Da

The representative blood level curves after intravenous administrations of $Da(MeS)_2$, $Da(PhS)_2$, $Da(GlS)_2$, $Da(HS)_2$ and Da are shown in Fig. 1—3. To ignore the molecular weight differences the amount of $Da(MS)_2$ and Da(MS) were represented in that of Da. Experiments were carried out at least three times for all drug forms and consistent patterns of blood levels were obtained. Every curve of the administered form of drug is apparently biexponential, which rationalizes two compartment open model[5] for any of these drugs. For instance numerical equations representing the blood concentrations of $Da(MS)_2$ and intact Da in Fig. 1, 2 and 3 are as follows, which is in μg/ml and t is in minutes.

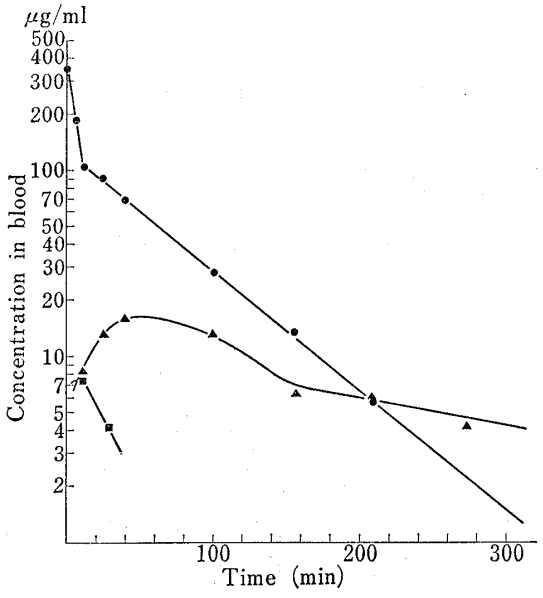


Fig. 1. Blood Concentration Changes of Drugs after Intravenous Administration of $Da(MeS)_2$

●: $Da(MeS)_2$, ■: Da(MeS), ▲: Da

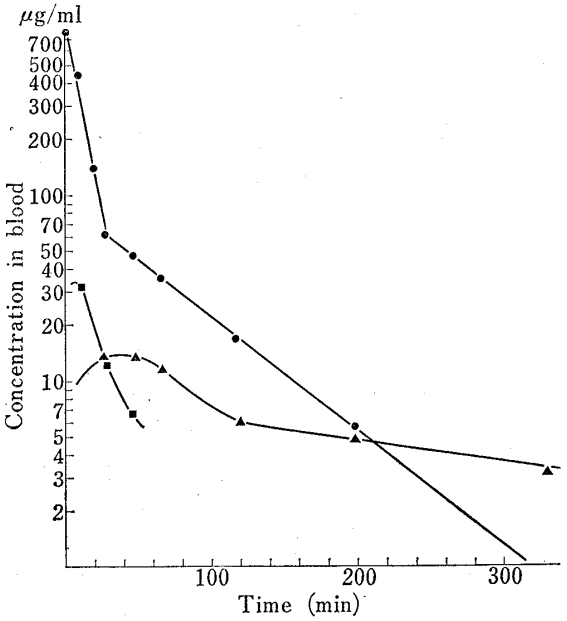


Fig. 2. Blood Concentration Changes of Drugs after Intravenous Administration of $Da(PhS)_2$

●: $Da(PhS)_2$, ■: Da(PhS), ■: Da

$$C_{Da(MeS)_2} = 240\, e^{-0.107t} + 132\, e^{-0.0152t} \quad (1)$$

$$C_{Da(PhS)_2} = 780\, e^{-0.124t} + 87.0\, e^{-0.0143t} \quad (2)$$

4) K. Ikeda, Y. Kurono, and T. Tukamoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 863 (1972).
5) S. Riegelman, J.C. Loo, and M. Rowland, *J. Pharm. Sci.*, **57**, 117 (1968).

$$C_{Da(GlS)_2} = 141\,e^{-0.0838t} + 81.3\,e^{-0.0103t} \quad (3)$$

$$C_{Da(HS)_2} = 205\,e^{-0.0922t} + 63.1\,e^{-0.00672t} \quad (4)$$

$$C_{Da} = 54.0\,e^{-0.0844t} + 73.0\,e^{-0.00207t} \quad (5)$$

The rate constants of the two compartment models for each administered drug form were calculated by Perl's[6] and Riegelman's[5] method and are listed in Table I. All the values in Table I are the means obtained in 3 or 4 rabbits. The values k_{12} and k_{21} are first order rate constants of transference from central to peripheral compartment and that from peripheral to central compartment respectively. The value of k_{el} is the elimination rate constant from central compartment. The k_{el} value for intact Da is about 10 fold smaller than those of water soluble derivatives. The apparent distribution volumes of the central compartment are also shown in Table I. The distribution volume of Da is larger than those of MSDs as is expected from the hydrophobic character of intact Da.

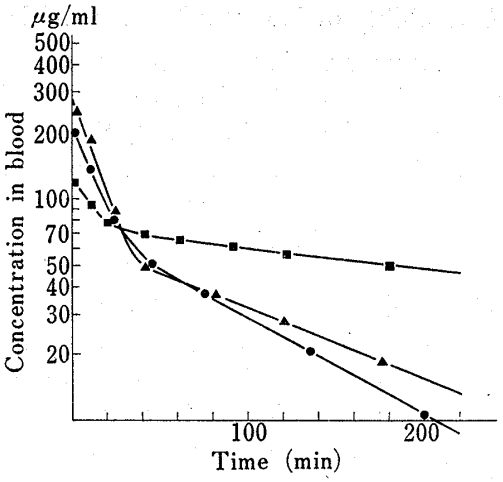


Fig. 3. Blood Concentration Changes of Da $(GlS)_2$ (●), Da $(HS)_2$ (▲) and Intact Da (■) Administered Intravenously

TABLE I. Rate Constants of Two Compartment Model for Various Da MSDs and Da (min^{-1}) and Distribution Volumes of Central Compartment (ml/kg)

	k_{12}	k_{21}	k_{el}	Distribution volume of central compartment
$Da(MeS)_2$	6.38×10^{-2}	6.67×10^{-2}	4.22×10^{-2}	138
$Da(PhS)_2$	6.04×10^{-2}	2.44×10^{-2}	6.51×10^{-2}	232
$Da(GlS)_2$	3.37×10^{-2}	3.72×10^{-2}	2.31×10^{-2}	347
$Da(HS)_2$	4.82×10^{-2}	2.22×10^{-2}	2.78×10^{-2}	178
Da	6.15×10^{-2}	8.63×10^{-2}	4.40×10^{-3}	570

In Fig. 1 and 2, the blood levels of the hydrolyzates, Da(MS) and Da, are also presented, where the level of Da(MS) is low and the drug is eliminated rapidly. The blood levels of Da(MS) attain their maxima so early as would not be expected from the *in vitro* kinetic data though accurate maxima were not observed. The 1st and 2nd step hydrolysis rate constants of $Da(MeS)_2$ determined at 37° in the rabbit whole blood are 8.05×10^{-3} and 7.73×10^{-3} min^{-1} and for $Da(PhS)_2$ are 8.17×10^{-3} and 7.55×10^{-3} min^{-1} respectively. From these rate constants it can be calculated that the time at which Da(MS) concentration attains maximum supposing simple consecutive hydrolysis in whole blood is about 130 minutes for these derivatives. In the case of $Da(GlS)_2$ and $Da(HS)_2$ no detectable amount of Da(GlS), Da(HS) nor Da was found in blood after intravenous administrations. For $Da(GlS)_2$ and $Da(HS)_2$ the 1st and 2nd hydrolysis rate constants *in vitro* were also too small to estimate experimentally. These results verify our suspicion that the pharmacological availability of Da from $Da(GlS)_2$ (promin) or $Da(HS)_2$ is negligibly small.

For the full interpretation of the pharmacokinetic changes in biophase, six-compartment model[7] is at least necessary providing two compartments for $Da(MS)_2$, Da(MS) and Da respec-

6) W. Perl, *Intern. J. Appl. Radiation Isotopes*, **8**, 211 (1960).
7) S.A. Kaplan, M. Lewis, M.A. Schwartz, E. Postma, S. Cotler, C.W. Abruzzo, T.L. Lee, and R.E. Weinfeld, *J. Pharm. Sci.*, **59**, 1569 (1970).

tively. However every rate constant in this model could not been determined because the blood level of Da(MS) was too low and irresponsible for precise calculation. It was attempted to synthesize pure Da(MeS) or Da(PhS) to obtain pharmacokinetic data on these derivatives, but $Da(MS)_2$ was mingled in any trial.

Availability of Parental Da from MSD

Among various evaluation methods of availability of drugs, the comparison of the area under the blood level curves of Da liberated from the derivatives, $S_{\text{Da from MSD}}$, with that of the intact Da administered, $S_{\text{intact Da}}$, may be appropriate for the chemotherapeutics. The value defined as follow was estimated.

$$\text{Availability} = \frac{S_{\text{Da from MSD}} \times \text{Dose}_{\text{intact Da}}}{S_{\text{intact Da}} \times \text{Dose}_{\text{MSD}}} \qquad (6)$$

The found values were 0.233 and 0.164 for $Da(MeS)_2$ and $Da(PhS)_2$ respectively, where Dose_{MSD} was given in the equivalent amount of parental Da per kg. weight. The areas where the actual blood levels were not obtained experimentally were estimated from the extraporation of the logarithmically linear decrease of Da.

Another trial for the evaluations of the availability are carried out according to following deconvolution calculations.[8–10]

$$M(t) = \int_0^t R(t-\theta)F(\theta)d\theta \qquad (7)$$

where $M(t)$ and $F(t)$ are the blood concentration of Da liberated from $Da(MS)_2$ and that of the intact Da respectively and $R(t-\theta)$ is the liberation rate of Da from $Da(MS)_2$ in biophase. For $F(t)$, the calculated blood concentrations of Da administered for the equivalent amount of the derivatives were used. The deconvolution calculation was carried out by rectangular method to 300 minutes with interval of 10 minutes and 300 minutes was enough for convergence. For $Da(MeS)_2$ and $Da(PhS)_2$, the values were 0.342 and 0.172 respectively. In the case of $Da(GlS)_2$ (promin) and $Da(HS)_2$, these calculations were impossible because no detectable blood levels of Da were found. As was pointed out in the previous paper[3] $Da(MeS)_2$ and $Da(PhS)_2$ may be better derivatives from the stand point of Da availability compared to promin or $Da(HS)_2$.

8) H. Branson, *Bull. Math. Biophy.*, **8**, 159 (1946); *idem*, *ibid.*, **9**, 93 (1947).
9) H. Branson, *Arch. Biochem. Biophy.*, **36**, 48 (1952); *idem*, *ibid.*, **36**, 60 (1952).
10) *a*) M. Hanano, *Chem. Pharm. Bull.* (Tokyo), **15**, 994 (1967); *b*) H. Nogami and M. Hanano, *ibid* **15** 1002 (1967).