ニワトリ排泄物中のスルファジメトキシン脱メチル化代謝産物の同定

誌名	Japanese journal of veterinary science
ISSN	00215295
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巻/号	48巻5号
掲載ページ	p. 999-1002
発行年月	1986年10月

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Identification of Desmethyl Metabolite of Sulfadimethoxine in Chicken Excreta

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(Received 22 October 1985/Accepted 26 May 1986)

ABSTRACT. An unknown metabolite of sulfadimethoxine (SDM) in chicken excreta was identified as N^1-(2-methoxy-6-hydroxy-4-pyrimidinyl) sulfanilamide by mass spectrometry, infrared spectroscopy, and etc. It was found to be a principal metabolite in the excreta of chicken that received SDM and considered as the causal substance of the nonlinear pharmacokinetics of SDM in chicken. This is the first report, in which the compond is identified as the major metabolite of SDM.—KEY WORDS: chicken, desmethylsulfadimethoxine metabolite, N^1-(2-methoxy-6-hydroxy-4-pyrimidinyl) sulfanilamide.

Jpn. J. Vet. Sci. 48(5): 999–1002, 1986

A metabolite of sulfadimethoxine (SDM) in my previous study on the nonlinear pharmacokinetics of SDM [2] (UK-metaolite) was found, but not identified in the excreta of chickens after the intravenous administration of SDM. All the other SDM-metabolites have been known as the conjugates, whereas the UK-metabolite was first isolated from the free fraction of the SDM-metabolite. Further, the UK-metabolite was the major metabolite (about 40%) in the excreta of the chickens after 10 mg/kg in-

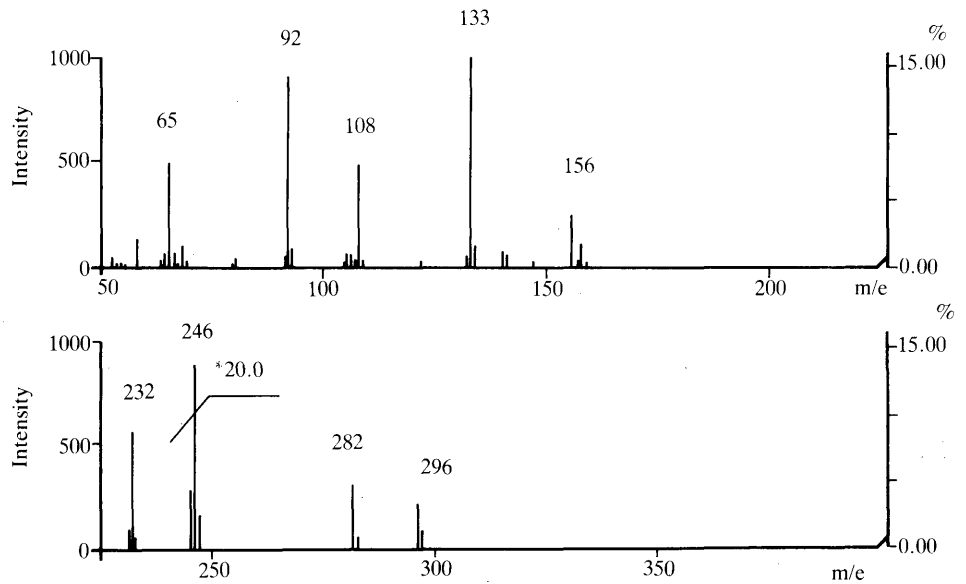


Fig. 1. Electron impact mass spectrum of the unknown metabolite of sulfadimethoxine. Ion source temperaure: 230°C, Sample temperature: about 180°C, Ionization current: 300 μA, Electron energy: 70 eV.

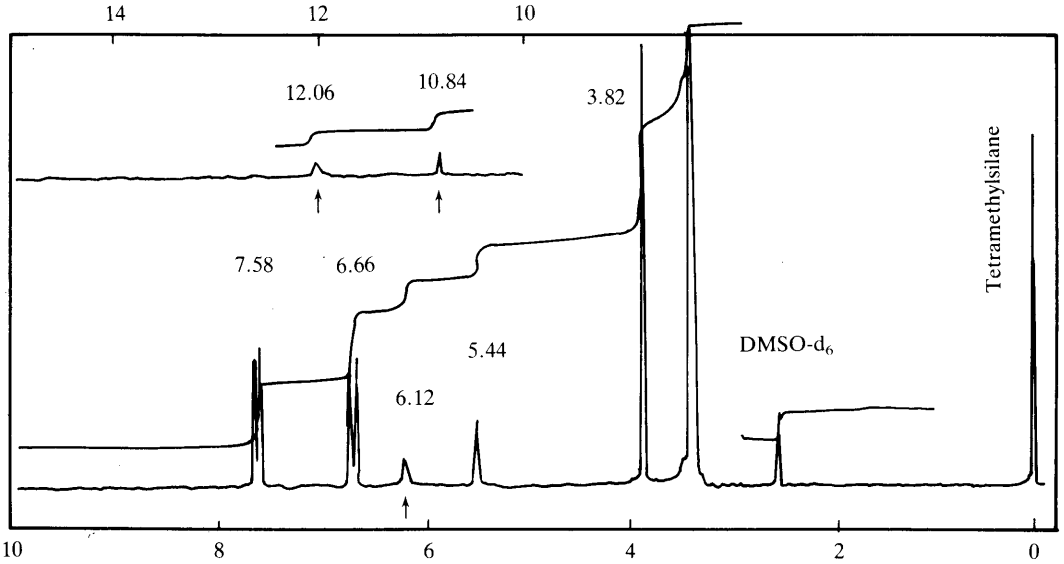
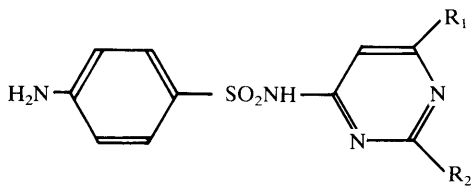


Fig. 2. H^1-NMR spectrum (DMSO-d_6) of the unknown metabolite of sulfadimethoxine. δ=3.82 (3H, s, OCH_3), 5.44 (H, s, pyrimidine-5-H), 6.66 (2H, d, J=8.0 Hz, phenyl-3, 5-H), 7.58 (2H, d, J=8.0 Hz, phenyl-2, 6-H). The peaks (δ=6.12, 10.84, 12.06) were disappeared by the addition of D_2O.



	R_1	R_2
SDM	OCH_3	OCH_3
6-OH	OH	OCH_3
2-OH	OCH_3	OH

Fig. 3. Chemical structure of sulfadimethoxine (SDM). N^1-(2-methoxy-6-hydroxy-4-pyrimidinyl) sulfanilamide (6-OH) and N^1-(2-hydroxy-6-methoxy-4-pyrimidinyl) sulfanilamide (2-OH).

travenous administration. The UK-metabolite was also suggested as the causal substance of the nonlinear pharmacokinetics of SDM.

In the present study, the UK-metabolite in the excreta was separated by thin layer chromatography (TLC) [2], extracted with ethyl acetate from the TLC plate, and the extracts were evaporated to dryness to afford pale brown crystals. The electron impact mass spectral data (Nippondenshi Co., JMS-D 300) on the UK-metabolite indicated a molecular weight of 296, suggesting the demethylation of one methoxy group of SDM (Fig. 1). The H^1-NMR spctrum (Varian Associates Inc., XL-200) and its deuterium exchanged spectrum of the UK-metabolite indicated that the metabolite contained one methoxy and one hydroxy group (Fig. 2). The results indicate that the UK-metabolite is a partially demethylated compound of the dimethoxy pyrimidine moiety of SDM.

To confirm the chemical structure, the UK-metabolite was compared with authentic N^1-(2-methoxy-6-hydroxy-4-pyrimidinyl) sufanilamide (6-OH) synthesized by Sano *et al.* [1] and N^1-(2-hydroxy-6-methoxy-4-pyrimidinyl) sulfanilamide (2-OH), both of which were chemically derived from SDM (Offered from Dai-ichi Seiyaku Co., Ltd.) (Fig. 3). It was shown that the UK-metanbolite was identical to the authentic sample of 6-OH by i) the Rf values on TLC, ii) mixed melting point determination

Table 1. Rf-values, melting point and solubility of the isolated unknown metaboite (UK-metabolite), N^1-(2-methoxy-6-hydroxy-4-pyrimidinyl) sulfanilamide (6-OH) and N^1-(2-hydroxy-6-methoxy-4-pyrimidinyl) sulfanilamide (2-OH)

	Rf-value		Melting point	Solubility		
	1[a)]	2[b)]	(°C)	Acetone	Chloroform	Water
UK-metabolite	0.62	0.43	243–245	freely soluble	slightly soluble	practically insoluble
6-OH	0.62	0.43	245	freely soluble	slightly soluble	practically insoluble
2-OH	0.33	0.11	172	practically insoluble	practically insoluble	slightly soluble

a) Developed with the mixture of chloroform, methanol (2:1) to migrate 10 cm.
b) Developed with acetone to migrate 2 cm. After dried, developed again with the mixture of n-butyl alcohol, chloroform, diethyl ether and water (4:8:2:0.1) to migrate 18 cm.

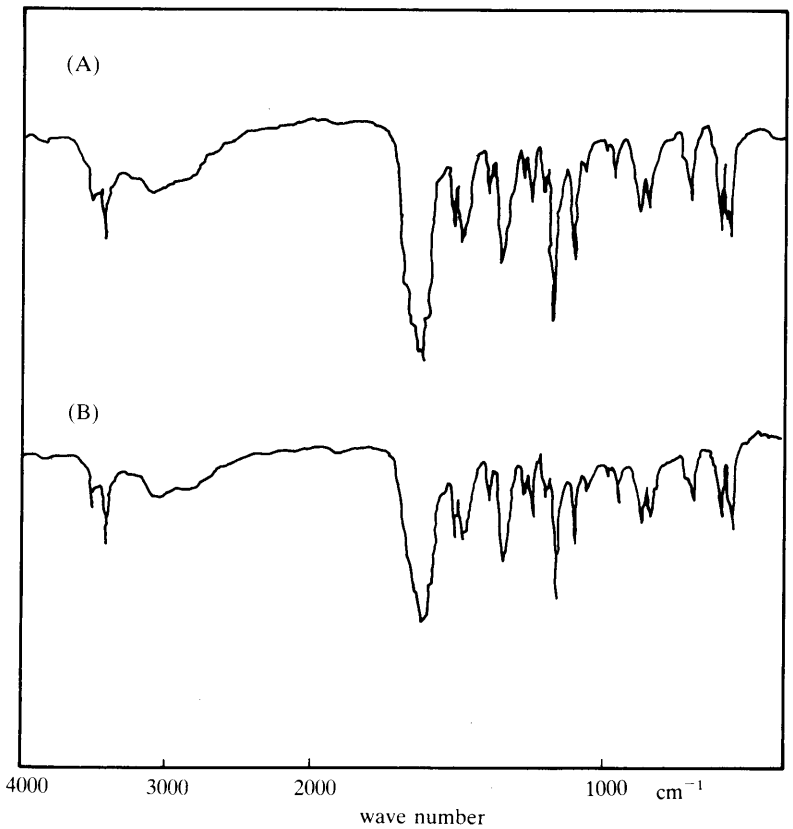


Fig. 4. Infrared spectra of the isolated unknown metabolite (A) and chemically derived N^1-(2-methoxy-6-hydroxy-4-pyrimidinyl) sulfanilamide (B).

(Yamato Kagaku Co., Ltd., MP-21) and iii) solubilities (Table 1). Finally, the structure of the UK-metabolite was established to be 6-OH by comparison of infrared spectra (Nissei Sangyo Co., Ltd., Hitashi 260–30) (Fig. 4).

This is the first report on the determination of the chemical structure of a SDM-metabolite isolated from chicken excreta as one containing 6-OH groups.

REFERENCES

1. Sano, H., Ooya, H., Takemoto, K., Maruyama, H., and Iwata, K. 1961. *Chemotherapy* 9: 261–265.
2. Takahashi, Y. 1986. *Jpn. J. Vet. Sci.* 48: 105–109.

要　約

ニワトリ排泄物中のスルファジメトキシン脱メチル化代謝産物の同定：高橋美幸（農林水産省動物医薬品検査所）――ニワトリにスルファジメトキシン（SDM）投与後の主な排泄物で，SDMの非線形動態の原因と考えられる未知の代謝産物が，N^1－(2－methoxy－6－hydroxy－4－pyrimidinyl) sulfanilamideであることを，マススペクトル，赤外吸収スペクトル等により明らかにした。