Sulfamylurea Hypoglycemic Agents. II. Drug Dynamic Studies

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The aqueous solubilities, lipid–water partition ratios, and ionization constants of a series of sulfamylurea hypoglycemic agents are reported, together with the metabolism and excretion of these compounds in man and the dog. The physiological disposition of these compounds is related to their physical properties in terms of established drug dynamic concepts.

In recent years, considerable emphasis has been placed on understanding the role which physical properties play in determining the physiological fate of a drug. After oral administration, a drug must be absorbed from the gastrointestinal tract into the blood, by which it is distributed to the various body tissues, and ultimately is excreted or metabolized. It has been recognized that, between analogous or closely related compounds, these processes (absorption, distribution, metabolism, and excretion) frequently can be correlated with the lipid–water partition ratio, solubility, ionization constant, etc., of the compounds.[1–7] Attempts to describe these processes quantitatively, using the mathematics of chemical kinetics,[8–10] have been applied recently in studies on antibacterial sulfonamides[11,12] and tetracycline antibiotics.[13]

In studies on the hypoglycemic sulfonylureas, it was recognized that the magnitude of the hypoglycemic effect was related to the concentration of the drug in blood.[14,15] Clinical potency, therefore, being compounded of both intrinsic activity and the time over which that activity is manifested, is dependent upon the plasma half-life of the drug.[16] It was anticipated that the related series of sulfamylureas would reveal a similar relationship and that drug dynamic factors and the physical and chemical properties influencing plasma half-life would be an important aspect of the study of their pharmacology. The preparation and hypoglycemic activity of these compounds have been detailed in a previous paper.[17] Concurrently with synthetic work, the physical–chemical factors that it was believed would influence the physiological disposition of these compounds were studied. These factors, together with the metabolism and excretion of these agents in the dog and man are reported in this paper.

Materials and Methods

Plasma, urine, and fecal samples were analyzed for drug and metabolites by methods previously described.[18] The pK_a was determined either by titration in 50% aqueous dioxane[19] or by the method of solubility in buffer solutions of varying pH.[20–23] All pK_a determinations were made at 25°. Relative lipophilicities were determined in two ways. The R_f of the test compound was measured, relative to a known standard, in a descending chromatographic system (benzene saturated with propylene glycol–2% acetic acid[24]) on Whatman No. 4 paper. The papers were sprayed with KOCl–KI–starch solution to make the spots visible. Alternatively, the partition ratio of the compound between 0.1 N HCl and cyclohexane was measured (at concentrations of 10–100 γ/ml.). This system gave partition ratios such that the concentrations of sulfamylurea in both phases could be analyzed by the available techniques.[18] In the chloroform–0.1 N HCl system, the partition ratios of the majority of the compounds studied were so high that concentrations in the aqueous phases were below the assay capabilities (5 γ/ml.).

Animal studies were carried out in fasted unanesthetized mongrel dogs of both sexes. Drugs were administered in solution (intravenously) or in a gelatin capsule (orally), except for compounds of very low solubility (VI and VIII, see Table I) which were ground in water in a tissue homogenizer and administered in suspension by stomach tube. Blood samples were drawn from the brachial vein and transferred to heparinized tubes. The animals were housed in metabolism cages with free access to water. Food was withheld for 24 hr. preceding drug administration. Urine and feces were collected from the cages. For investigation of the dynamic properties of the sulfamylureas in man,[25] the compound (1 g.) was administered orally to apparently healthy male prisoner volunteers in the fasting state. Blood samples were drawn by venipuncture and transferred immediately to heparinized tubes; drug plasma half-life was mathematically derived from measurements of plasma drug concentrations.[26] Urine was collected for a period of 72 hr. and stored at 4° until analyzed.

Results and Discussion

The physical properties of the compounds investigated in this study are shown in Table I, together with their plasma half-lives and extent of urinary excretion in the dog. Chlorpropamide (XVI) was studied as a

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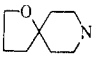
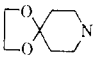
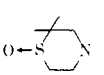
TABLE I

PHYSICAL AND PHARMACODYNAMIC PROPERTIES OF THE SULFAMYLUREAS

$R_1SO_2NHCONHR_2$

No.	R_1	R_2	Solubility, mg./ml. pH 7.0[a]	Solubility, mg./ml. Water	pK_a	Lipophilicity R_f	Lipophilicity Partition	Plasma half-life, hr.	Urinary recovery, % Oral	Urinary recovery, % Intravenous
I			6.47	1.32	5.6	0.39	0.19	10–14	20	31
II			1.80	0.18	6.1	0.48	0.45	7–11	32	25
III		$CH_2CF_2CF_3$			4.8[b]	0.13	0.03	0.5–1		60
IV		$CH_2CF_2CF_3$			4.8[b]	0.17	0.02	1–2		56
V			0.89	0.14	6.4[b]	0.58	3.96	4–8	38	38
VI			0.07	0.00	6.2	0.68		3–4	11[c]	21
VII		$CH_2CF_2CF_3$			5.6[b]	0.30	0.03	7–9		30
VIII			0.00	0.00	6.4[b]	0.79		2.5–3.5	7[c]	25
IX			0.35	0.05	6.4	0.50	1.30	2–3	15	31
X		$CH_2CF_2CF_3$			5.4[b]	0.29	0.03	6–9		47
XI			0.86	0.10	6.0[b]	0.43	0.49	5–9	12[d]	24[d]
XII			0.92	0.10	6.0	0.47	1.15	4		45[e]
XIII			>1.0	0.73	5.1[b]	0.05		<1		60
XIV					6.3[b]	0.55	1.79	1–2		55[f]
XV						0.10		<1		62
XVI[g]		$CH_2CH_2CH_3$	6.13	0.33	4.8	0.17	0.16	20–25		21

[a] Citric acid-disodium phosphate. [b] Measured in 50% dioxane and corrected to aqueous value (Materials and Methods). [c] Administered as sodium salt. [d] Partially recovered as piperidone. [e] Recovered as sulfoxide. [f] Chlorpropamide.

reference compound. Many of the compounds in the sulfamylurea series had aqueous solubilities too low to permit measurement of pK_a by the buffer solubility method,[20–23] but all were sufficiently soluble for titration in 50% aqueous dioxane. The "apparent" pK_a of the sulfamylureas in this system was about 1.7 units higher than the pK_a measured in the fully aqueous system. This correction, observed both in the sulfamylureas reported in this paper and in a large number of related compounds,[27] was applied to any pK_a determined in 50% aqueous dioxane to estimate the pK_a in an all aqueous system. The ratios of the cyclohexane–dilute acid partition coefficients of the sulfamylureas were relatively the same as the ratios of their R_f indices in the paper chromatographic system, in the range R_f 0.2–0.6. Outside these limits, the correlation was limited, probably owing to the intrusion of other factors (possibly adsorption on the paper) into the R_f value. However, since the partition ratios of the sulfamylureas in the chloroform–dilute acid system were so high (approximately 10–1000), the differences noted in the cyclohexane–dilute acid ratio are probably without physiological significance. Partition ratios of the magnitude seen in the chloroform–dilute acid system are such that rapid penetration of physiological lipoidal

(27) E. H. Wiseman and R. L. Wagner, unpublished observations.

TABLE II

EFFECT OF PHYSICAL STATE OF VI AND VIII[a] ON ABSORPTION IN THE DOG

Route of administration	Physical form	2-hr. plasma drug concn., γ/ml. VI	VIII	24-hr. urinary recovery, % VI	VIII	24-hr. fecal recovery, % VI	VIII
Intravenous	Solution	70	54	9	25		8
Oral (capsule)	Crystalline	6	0	2	6	88	80
Oral (capsule)	Powder	29	0	3	6	45	65
Oral (capsule)	Sodium salt	40	15	9	7	27	50
Oral (suspension)	Sodium salt	73	27	11			

[a] 25 mg./kg.

TABLE III

PEAK PLASMA DRUG CONCENTRATIONS AND PER CENT URINARY EXCRETION IN HUMAN SUBJECTS RECEIVING SULFAMYLUREAS[a]

No.	No. of subjects	Peak plasma drug concn. Time after dose, hr.	Peak plasma drug concn. Concn., γ/ml.	48-hr. urinary recovery, % Unchanged drug	Sulfamide metabolite	Amine metabolite
I	5	4	90	14		
II	9	3	50	16		4
VI	10	4	14	6		
VI[b]	5	1	85	20	19	
VIII[c]	6	3	14	10	2	3
IX	5	3	28	14	63	6
XI	10	3	28	23[d]		6

[a] 1 g. orally. [b] Administered as solution of sodium salt in 200 ml. of water. [c] Administered as sodium salt. [d] Partially recovered as piperidone.

phases would be expected, and this step would not be rate limiting in the diffusion process.

After oral administration, the weakly acidic (pK_a = 4.8–6.4) sulfamylureas, once dissolved in the contents of the gastrointestinal tract, would be expected to be swiftly absorbed. With two exceptions, all the compounds studied had water solubilities such that solution and absorption occurred rapidly, as evidenced by approximately equivalent peak plasma drug concentrations and urinary recoveries after oral and intravenous administration. The absorption of the two very sparingly soluble (less than 10 γ/ml.) compounds VI and VIII was profoundly affected by the physical form administered (Table II). Whereas intravenous administration (25 mg./kg.) produced initial plasma drug concentrations typical of the series (50–70 γ/ml.), oral administration of the crystalline compound resulted in low plasma concentrations, and most of the drug was recovered in the feces. Absorption was improved, to some extent, by powdering the drug, and still further by administering it as the sodium salt. When the drug, either as the free acid or as the sodium salt, was finely ground in a tissue homogenizer before administration in suspension by stomach tube, absorption was further enhanced. Plasma concentrations of VI, following oral administration of the finely ground sodium salt, were comparable to those observed after intravenous administration.

These results parallel those observed by other workers in studies on the hypoglycemic sulfonylurea, tolbutamide.[28] Following oral administration to human subjects of the sodium salt of tolbutamide, which dissolves in acidic media nearly 10^4 times as rapidly as the free acid, plasma drug concentrations approached those obtained after intravenous administration. In contrast, orally administered tolbutamide gave lower but more prolonged plasma drug concentrations. In studies in human subjects with the sulfamylureas, the influence of physical state on oral absorption was comparable to that observed in the dog (Table III). Compound VI, administered as the acid, gave a low peak-plasma concentration; however, administered as the sodium salt, it swiftly gave high plasma concentrations. Compound VIII, administered as the sodium salt, gave only low plasma concentrations, which by analogy with the dog were most probably the result of incomplete absorption. Thus, even a drug with as low a solubility as VI was rapidly and completely absorbed, when the material was administered in a form which presented the maximum possible surface area so that rate of solution was maximal.[29,30] However, even administration as the finely ground sodium salt, a form which would be expected to have a maximal rate of solution, could not offset the extremely low aqueous solubility of VIII, and this compound was incompletely absorbed.

The sulfamylureas were eliminated from plasma by both excretion and metabolism. Unless the compound contained a metabolically more vulnerable center, it was metabolized by cleavage to the related sulfamide

$$R_1\text{⌒}NSO_2NHCONHR_2 \longrightarrow R_1\text{⌒}NSO_2NH_2 + H_2NR_2$$

and primary amine. The sulfamide, in general, was resistant to further metabolism and was excreted as such, but the amine moiety was apparently extensively degraded since very little was detectable in the urine. The metabolic fate of the compounds that were studied in both species appeared to be essentially similar in man and the dog. Further evidence of similarity between the species was obtained from a comparison of plasma half-lives. In dogs, this was determined after intravenous administration of the drug. In man, the plasma drug concentrations following oral administration were subjected to kinetic analysis to derive plasma half-life.[26] It can be seen (Table IV) that for those compounds from which determinations could be

(28) J. G. Wagner, *J. Pharm. Sci.*, **50**, 359 (1961), and references therein.

(29) E. Nelson, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 96 (1959).

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TABLE IV

PLASMA HALF-LIVES AND PER CENT EXCRETION OF SULFAMYLUREAS IN MAN AND THE DOG

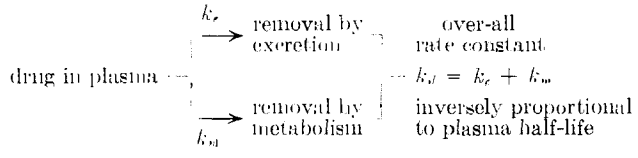
No.	Plasma half-life, hr. Dog	Plasma half-life, hr. Man	48-hr. urinary recovery, %[a] Dog	48-hr. urinary recovery, %[a] Man
I	10–14	10	20	14
II	7–11	6	32	16
VI	3–4	4.5	11	20
VIII	2.5–3.5		7	10
IX	2–3	2.5	15	14
XI	5–9	2.5	12	13

[a] After oral administration.

made, the plasma half-life and extent of urinary excretion of unchanged drug were essentially similar in man and the dog. No estimate of the plasma half-life of VIII in man could be made since, because of poor absorption, plasma drug concentrations were below the limit of accurate determination. Compound XI, a cyclic ketal derivative, showed a shorter half-life in man than in the dog. Paper chromatography of human urine extracts showed that the preponderance of urinary material, both as sulfamylurea and its sulfamide metabolite, was in the piperidone form, the ketal having been hydrolyzed. It is possible that in man, enzymes capable of degrading XI to the piperidone are more active than in the dog, and this may account for the more rapid disposal of the drug in man. However, incubation of XI in simulated gastric juice led to considerable hydrolysis to the piperidone form in 4 hr.,[31] and it is possible that the urinary ketonic material resulted from hydrolysis prior to absorption, rather than from enzymatic metabolism.

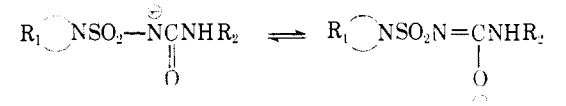
In this sulfamylurea series, sulfoxidation appeared to be a more rapid metabolic process than cleavage to the sulfamide. The thiomorpholinosulfamylureas XII and XIV, studied in the dog only, were excreted as the sulfoxides. Further oxidation to the sulfone did not occur, administered sulfoxides being rapidly excreted unchanged in the urine.

As outlined previously, clinical potency of the sulfonylurea hypoglycemic agents is partially a function of drug plasma half-life.[16] Since one of the aims of this research was sulfamylureas with extended plasma half-lives, a quantitative relationship between physical properties and plasma half-life could be of great value in guiding synthetic work. The rate constant defining plasma drug half-life is a summation of the rate constants for two separate physiological processes, namely, excretion and metabolism. Attempts to rationalize



the summation of these two processes in terms of the physical properties of the drug may be unsuccessful unless it is recognized that each process has a different dependence on physical properties.

The exact nature of the renal excretion of the sulfamylureas is as yet uninvestigated. The compounds are extensively bound to plasma proteins (75–99%),[32] and it must be assumed that the sulfamylureas can be introduced into tubular urine by both filtration at the glomerulus and by tubular secretion. Considering the high lipophilicity of the sulfamylureas, it is almost certain that reabsorption from tubular urine occurs, to an extent dependent on the degree of ionization of the



molecule in tubular urine.[33] The more acidic (low pK_a) compounds, being more extensively ionized in tubular urine, would be expected to be less efficiently reabsorbed.

Much evidence is now available to demonstrate that the liver is the organ usually responsible for the destruction of organic compounds foreign to the animal.[5] Many of the enzymes responsible for metabolic reactions have been shown to be present in the supernatant fraction of liver homogenate which remains after centrifugation at 9000*g*.[34,35] These enzymes can be visualized as being protected by a lipid-like sheath, and since compounds of high lipophilicity are generally more rapidly degraded than are more hydrophilic analogs, the rate-limiting step in the metabolic process for some series of compounds has been postulated as being rate of diffusion through this lipid barrier.[6,36] However, since all of the compounds in the sulfamylurea series are of high lipophilicity, and differences between them are actually small, it seems likely that other properties may be the controlling factors in their relative rates of metabolism.

Two steps in the metabolic process can be envisaged: diffusion to the site of metabolism, followed by cleavage at that site. If penetration of un-ionized drug to the intracellular enzyme site is rapid, it would not be the major factor controlling the rate of metabolism, and rate of cleavage would be the over-all rate-controlling step in the removal of sulfamylureas by metabolism. By analogy with chemical hydrolysis,[18] metabolic attack by some nucleophilic moiety is most likely to occur at the carbonyl function of the sulfamylurea. In the ionized form, the electron density at that center would tend to resist attack, and the more acid sulfamylureas (low pK_a), being more highly ionized at physiological pH, would be less prone to metabolism. Increase in acidity, therefore, would be expected to increase plasma half-life by conferring resistance to metabolism, but as discussed previously, it may also tend to decrease plasma half-life by hindering reabsorption of the sulfamylurea from tubular urine. It would thus be expected that there should be an optimum range of ioni-

(31) XI, dissolved in U.S.P. simulated gastric juice to a concentration of 500 γ/ml., was incubated at 37°. Samples of the incubate were examined by paper chromatography[24] (Materials and Methods) for unchanged XI (R_f 0.4) and related piperidone [R_f 0.1; positive reaction to Zimmerman reagent: T. H. Kritchevsky and A. Tiselius, *Science*, **114**, 299 (1951)]. After 15 min. of incubation, no Zimmerman-positive material was present. After 4 hr. of incubation, considerable Zimmerman-positive material was present, together with a small amount of unchanged XI.

(32) Determined at 25° by equilibrium dialysis through Visking membranes against pH 7.4 phosphate buffer at plasma concentrations of 50–100 γ/ml.

(33) A. B. Gutman, P. G. Dayton, T. F. Yü, L. Berger, W. Chen, L. E. Sicard, and J. J. Burns, *Am. J. Med.*, **29**, 1017 (1960).

(34) B. B. Brodie, J. R. Gillette, and B. N. La Du, *Ann. Rev. Biochem.*, **27**, 427 (1958).

(35) J. Axelrod, *J. Pharmacol. Exptl. Therap.*, **117**, 322 (1956).

(36) L. E. Gaudette and B. B. Brodie, *Biochem. Pharmacol.*, **2**, 89 (1959).

zation constant for compounds in this series, which would strike a balance between metabolic stability and renal elimination.

Attempts to attain this balance in this sulfamylurea series met with varied results. The longest plasma half-lives were seen in the compounds in the morpholine series; I (pK_a = 5.6) exhibited a plasma half-life in the dog of 10–14 hr., and approximately 30% of the drug was recovered unchanged in the urine after intravenous administration. Substitution in the morpholine ring had little effect on pK_a (II), but attempts to increase the acidity of compounds in this series by introduction of a pentafluoropropyl group in the place of a cycloalkyl group were successful.[17] The expected resistance to metabolism was obtained, but the increase in ionization constant (III and IV, pK_a = 4.8) was such that these compounds, being extensively ionized in tubular urine, were probably poorly reabsorbed and consequently rapidly excreted. Plasma drug half-life decreased to 1–2 hr. and about 60% of the drug was recovered unchanged in the urine.

Compounds in the piperidine series were of higher pK_a than their morpholine analogs, and, as was expected, proved to be relatively vulnerable to metabolism. VI (pK_a = 6.2) had a plasma half-life of 3–4 hr. and was extensively metabolized, less than 25% being recovered unchanged in the urine. The same extensive metabolism was seen in VIII (pK_a = 6.4, plasma half-life 2.5–3.5 hr.) and IX (pK_a = 6.4, plasma half-life 2–3 hr.). In this series also, an increase in acid strength was obtained by the introduction of the pentafluoropropylamine moiety.[17] Thus the analog of VI, VII (pK_a = 5.6), showed an increase in plasma half-life to 7–9 hr. This compound was more resistant to metabolism than VI, a reflection of increased acidity. Similar success was obtained with the pentafluoropropyl analog of VIII, X (pK_a = 5.4). This compound had a half-life in the dog of 6–9 hr., which appeared, from the urinary recovery of unchanged drug, to result from its comparative resistance to metabolism.

The broad generalizations concerning the effects of physical properties on physiological dynamics that have emerged from the study of this series of compounds are all consistent with well-established concepts of drug dynamics. Rate of oral absorption, related to rate of solution, is as much a function of the surface area of the compound presented for solution as it is of the absolute solubility. It appears that in a series such as the sulfamylureas, which in general have high lipid–water partition ratios, small changes in lipophilicity are without significance in control of physiological disposition. Increase in acidity confers resistance to metabolism. Since chemical hydrolysis is known[18] to occur by a mechanism facilitated by low degree of ionization (high pK_a), it is possible that the enzymatic process of metabolism is subject to similar control. Thus, relatively high acidity can lead to an extended drug plasma half-life. However, if the acidity of the compound becomes too high, the extent of ionization in tubular urine will be increased, and facile renal excretion will occur, presumably because tubular reabsorption is hindered.

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Sulfamylurea Hypoglycemic Agents. III. Tetrasubstituted Sulfamylureas and N-Sulfamylcarbamates

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Two new series of hypoglycemic agents have been synthesized: (1) tetrasubstituted sulfamylureas of the general formula $R_1R_2NSO_2NHCONR_3R_4$ (II) in which both R_1R_2N and NR_3R_4 are derived from secondary amines, and (2) sulfamylcarbamates $R_1R_2NSO_2NHCO_2R_5$ in which R_5 is cycloalkyl. Generally, the hypoglycemic activities of these compounds are somewhat less than those of previously described sulfamylureas represented by $R_1R_2NSO_2NHCONHR$ (I) in which NHR is derived from a primary amine. A simple method for the preparation of sulfonyl isocyanates is also described.

Earlier papers in this series[1,2] described the synthesis, hypoglycemic action, and drug dynamic properties of trisubstituted sulfamylureas of the general formula $R_1R_2NSO_2NHCONHR$ (I) wherein NHR is derived from various primary amines. These studies suggested that of two closely related sulfamylureas the more acidic analog will exhibit the longer half-life. Since longer half-lives were desirable in this series, efforts were made to increase the acidity of sulfamylureas.

Several modifications of the sulfonylurea structure can be made which will lower the pK_a. For example 1-butyl-1-methyl-3-(*p*-tolylsulfonyl)urea is about 2.5 times more acidic than its parent, 1-butyl-3-(*p*-tolylsulfonyl)urea (tolbutamide)[3] (see Table I). Reasoning that secondary amine derivatives might in general be more acidic than comparable primary amine derivatives, we undertook to synthesize tetrasubstituted sulfamylureas represented by $R_1R_2NSO_2NHCONR_3R_4$ (II) in which R_1R_2N is derived from piperidine or 4,4-dimethylpiperidine, and NR_3R_4 is derived from diverse secondary amines. A small series of N-sulfamyl-

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