Delarge J_17

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Chemistry and Pharmacological Properties of the Pyridine-3-sulfonylurea Derivative Torasemide

By J. Delarge

Summary: *Out of a series of pyridine-3-sulfonylureas with diuretic activity torasemide (1-isopropyl-3-{[4-(3-methyl-phenylamino)pyridine]-3-sulfonyl}urea) has been proved to be one of the most active derivatives.*

In the rat, urinary volume and electrolyte excretions increased linearily with the logarithm of the dose, thus resembling the profile of a high ceiling diuretic. Experiments by oral and intravenous routes indicated that torasemide was equally potent both by oral and parenteral administration. Compared to furosemide, torasemide was 9—40 times more potent on weight basis in the rat. For the same natriuretic effect, however, potassium losses with torasemide were significantly less than with furosemide. The diuretic effect of torasemide lasted longer compared to that of furosemide.

In accordance with the pharmacodynamic characteristics plasma elimination half-life of torasemide was about 1.5 h in the rat and bioavailability was nearly complete.

Torasemide was 98—99 % bound to plasma proteins. No in vitro interaction was found with the cumarine derivative warfarin.

Zusammenfassung: *Chemie und pharmakologische Eigenschaften des Pyridin-3-sulfonylharnstoffs Torasemid*

Aus einer Serie von Pyridin-3-sulfonylharnstoffen mit diuretischer Aktivität erwies sich Torasemid (1-Isopropyl-3-{[4-(3-methyl-phenylamino)pyridin]-3-sulfonyl}harnstoff) als eine der diuretisch aktivsten Substanzen.

Bei der Ratte steigerte Torasemid die urinäre Volumen- und Elektrolytausscheidung linear mit dem Logarithmus der Dosis und entsprach damit in der Wirkung einem Schleifendiuretikum. Nach oraler und i.v. Gabe zeigten gleiche Mengen von Torasemid die gleiche Wirksamkeit. Auf Gewichtsbasis war Torasemid bei der Ratte 9- bis 40mal stärker wirksam als Furosemid. Jedoch war die Kalium-Ausscheidung unter Torasemid bezogen auf den gleichen natriuretischen Effekt signifikant geringer als bei Furosemid. Der diuretische Effekt von Torasemid hielt im Vergleich zu Furosemid länger an.

In Übereinstimmung mit diesen pharmakodyamischen Eigenschaften betrug die Plasmahalbwertszeit bei der Ratte ca. 1,5 h, die Bioverfügbarkeit war nahezu vollständig. Torasemid wurde zu 98—99 % an Plasma-Proteine gebunden. Eine In-vitro-Wechselwirkung mit dem Cumarin-Derivat Warfarin konnte nicht nachgewiesen werden.

Key words: *Diuretics, loop- · Furosemide, pharmacology · Torasemide, chemistry, pharmacology*

1. Introduction

From the history of the development of the different classes of diuretic drugs, it becomes evident that the basic compounds in this field were discovered more by lucky chance than by rational design based on biological pathways or by clearly established structure-activity relationships (SAR).

This can be shown by some examples presented in Scheme 1 (see next page). The first diuretics, which were organomercurials, were developed around 1920 from the origin merbaphen which was first used as an antisyphilitic drug.

Around 1950, the inhibitors of the enzyme carbonic-anhydrase, e.g. acetazolamide and clofenamide were developed owing to a side effect of antibacterial sulfonamides, and the first representatives of the thiazides in 1957, chlorothiazide and hydrochlorothiazide have been synthesized by unexpected cyclisation of an aminochlorodisulfonamide derivated of carbonic-anhydrase inhibitors.

Later on, the so called loop diuretics were found by replacing isosterically a sulfonamide group by a carboxyl group in the disulfonamide molecule (furosemide) or by a serendipitous improvement of the old merbaphen (ethacrynic acid).

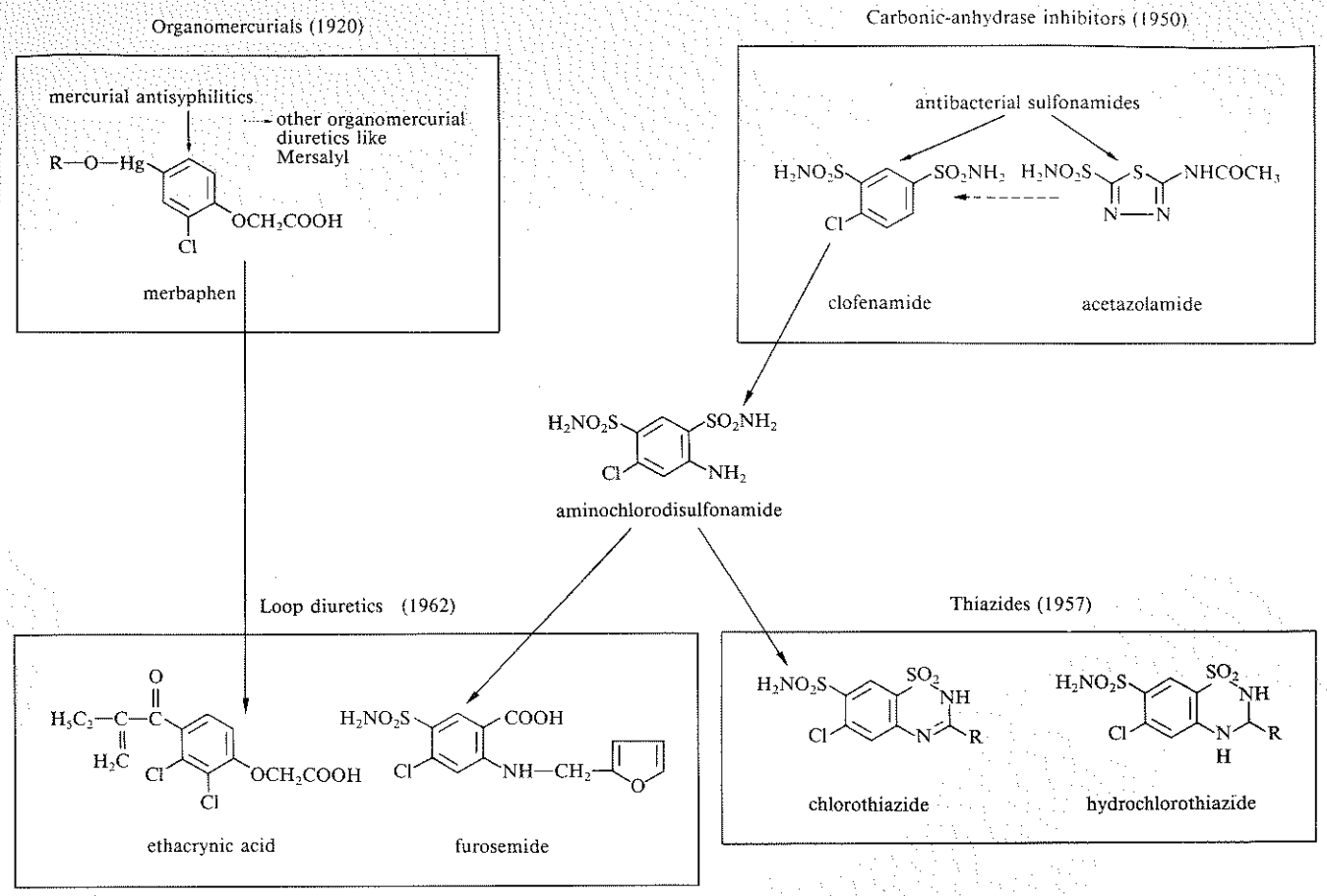
2. Chemistry

Originally, we started our work with the intention to find substances with antiinflammatory properties. In the beginning of 1973, a series of anilinopyridine-carboxylic acids was described as having antiinflammatory activity, one of them having also diuretic properties. Subsequently, our research efforts shifted to anilino-3-pyridinesulfonamides and sulfonic acids which also proved to have antiinflammatory properties.

Nearly at the same time, some patents claimed diuretic activity for similar compounds, but we were unable to confirm these results. However, we became more interested in compounds which could show diuretic activity, and we started a new chemical development with the specific aim to investigate this class of sulfonamides more in detail regarding SARs and diuretic activity. Roughly the steps which led us to the discovery of torasemide*) (1-isopropyl-3-{[4-(3-methyl-phenylamino)pyridine]-3-sulfonyl}urea) are given in Fig. 1 (see next page).

In the a.m. groups of compounds, diuretic activity was seen only among the 4-substituted amino-3-pyridine carboxylic acids and claimed but not observed among sulfonic acids and sulfonamides. We believed that the corresponding sulfonic acids were too highly ionized (polar) and most of the sulfonamides too poorly ionized (too weakly acidic) to have significant diuretic activity comparing with the good acting carboxylic acid. As we expected it, acylation of the sulfamoyl nitrogen atom provided compounds whose acidity lies in the range of carboxylic derivatives and many of the N-acyl-4-anilino-3-pyridine-sulfonamides were more diuretic in rats than chlortalidone and hydrochlorothiazide. The most active compounds were nearly as active as furosemide. One of them, the N-propionyl derivative of 4-(3-trifluoromethylani-

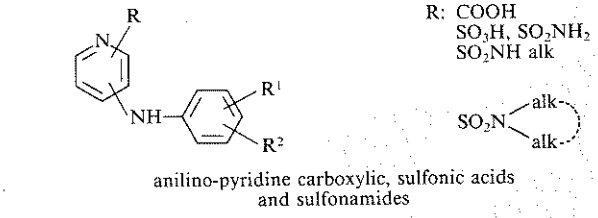
*) Manufacturer: Boehringer Mannheim GmbH, Mannheim (Fed. Rep. of Germany).

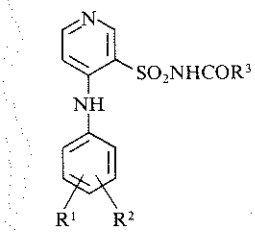


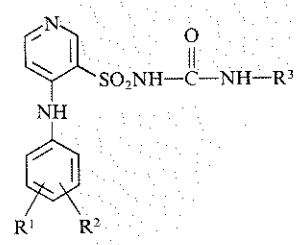
Scheme 1: History of diuretic drugs.

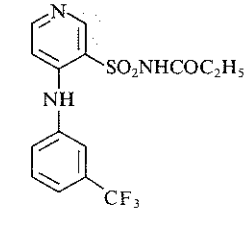
lino)-3-pyridinesulfonamide named gallosemide is shown in Fig. 2.

The finding that gallosemide was active in rats but inactive in man led us to conclude that the acyl function was being hydrolysed to the inactive deacyl compound in man but not in rats. Thus, we prepared branched analogs, where propionyl was replaced e.g. by isobutyryl and trimethylacetyl substituents. However, the same species difference in activity was observed with the compounds as occurred with gallosemide [1—8].




N-acyl-4-anilino-3-pyridine sulfonamides


4-anilinopyridine sulfonylureas


gallosemide

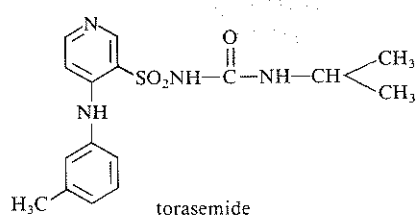

torasemide

Fig. 1: Rationale of the development of torasemide.

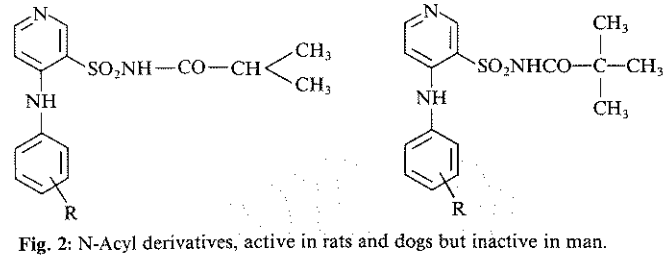
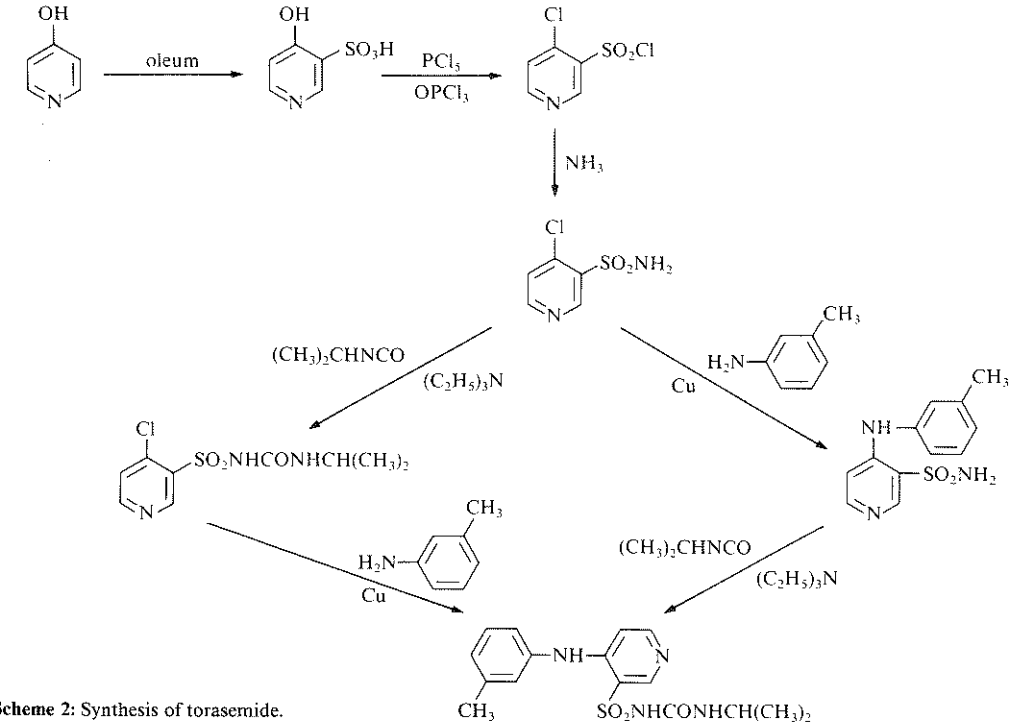


Fig. 2: N-Acyl derivatives, active in rats and dogs but inactive in man.

3. Synthesis of torasemide (Scheme 2, next page)

A further step in this research led us to seek other kinds of "acid enough sulfonamides derivatives" more resistant to biological hydrolysis and subsequently to synthesize the most active series in this class of compounds, the N-carbamoyl derivatives of the 4-amino-3-pyridinesulfonamides which, of course, are 4-amino-3-pyridinesulfonylureas.



Scheme 2: Synthesis of torasemide.

Compounds with a wide range of substituents on either the 4-amino or the sulfonylurea nitrogen atoms are highly active diuretics. Fortunately, these compounds do not exhibit the hypoglycemic activity which is characteristic of many sulfonylureas.

Starting from 4-hydroxypyridine, the key compound is 4-chloro-pyridinesulfonamide. At this step, torasemide can be prepared in principle by two different ways:

1. by condensation of 3 - sulfonamido - 4 - (3 - methylanilino)pyridine with isopropyl isocyanate by means of triethylamine around 95 °C;
2. condensation of m-toluidine with 1-isopropyl-3-(4-chloro-3-pyridyl)-sulfonylurea by means of Cu catalyst around 95 °C.

The chemical and crystal structures of torasemide are given in Fig. 3 [11].

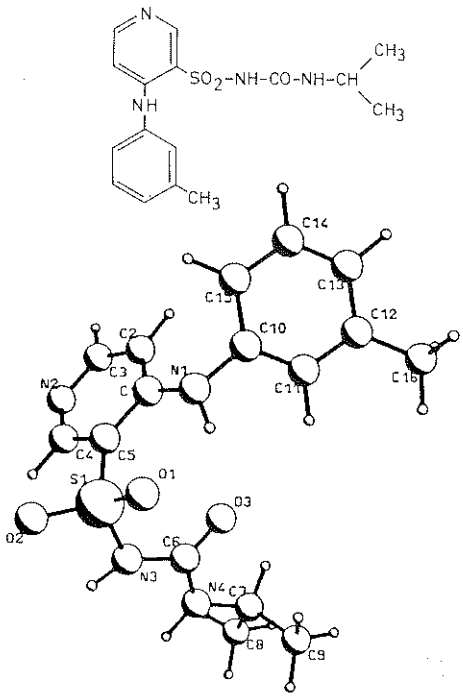


Fig. 3: Chemical and crystal structure of torasemide.

4. Structure-activity relationship (Table 1, next page)

In that first series of sulfonylureas, which are nearly all 4-anilino-3-pyridinesulfonylureas, maximal activity is generally achieved, as it is seen from Table 1 which records a selected list of compounds, when the R^1 substituent is isopropyl (note compounds **4, 11, 13, 16, 19, 21, 23, 30, 32, 34, 36, 39, 42, 43**). Groups that are larger or smaller, more or less branched, low saturated and so on are almost always less active. The tiourea analogs are always less active than their urea counterparts (compare compound **7** with **14**, **8** with **15**, **11** with **16**, and **24** with **27**).

With regard to the substituent on the 4-anilino nucleus (R^2 and R^3), one substituent is superior to two, 3-substitution is superior to 2- or 4-substitution and the relative activity-conferring effects of the substituents roughly are: $CH_3 \simeq Cl$, $CF_3 \simeq Br$, $F \simeq CH_3O$, $C_2H_5 \simeq NO_2$ (thus, we see, e.g. the following relative activities: compound **39** ≃ **11**, **25** ≃ **21**, **23** ≃ **36**, **42** ≃ **34**). A second substituent placed on the anilino nitrogen (R^4) is tolerated as shown by the activity of compound **28**; however, there are insufficient examples to explain its relative effect on activity.

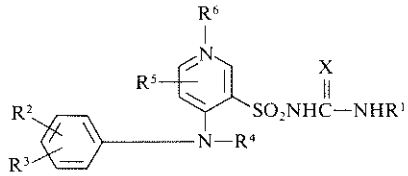
Limited investigation indicates that nuclear substitution of the pyridine ring (R^5) attenuates activity: thus compound **7** is more active than **12** and **11** is more active than **13**. Formation of the pyridine-N-oxides is detrimental, since compound **25** is more active than **26** and **39** is more active than **40**.

Three of the more active compounds in this series from the rat screen (compounds **8, 38** and **39** from Table 1) were evaluated in greater detail using the graded dose assay recorded in Table 2 (see next page). Each compound exhibited a marked and graded response to oral doses in the range of 1.25—10 mg/kg. Although the compounds were kaliuretic the Na/K ratio increased sharply over the eightfold increase in dose. It is also noteworthy that the (Na + K)/Cl ratio was nearly unity over the entire dose range.

A comparative oral rat diuretic study with three potent loop diuretics reveals the high potency of compound **39** (torasemide), which appears to be the most active member in this series. Fig. 4 (see next page) shows that torasemide possesses appreciable activity at 500 μg/kg and is considerably more diuretic than piretanide, furosemide and bumethanide in this assay [10].

It was also found that torasemide produces marked diuretic activity in dogs in doses of 25—200 μg/kg [10, 12, 13].

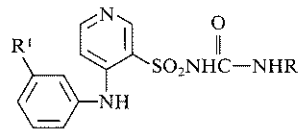
Table 1: 4-Anilinopyridine-3-sulfonylureas.



No.	R^1	R^2	R^3	R^4	R^5	R^6	X	Rat diuresis[a] (ml/kg/4 h)
1	Me	2-Cl	H	H	H	—	O	65
2	Et	2-Cl	H	H	H	—	O	75
3	Pr	2-Cl	H	H	H	—	O	43
4	i-Pr	2-Cl	H	H	H	—	O	72
5	Bu	2-Cl	H	H	H	—	O	56
6	t-Bu	2-Cl	H	H	H	—	O	11
7	Me	3-Cl	H	H	H	—	O	76
8	Et	3-Cl	H	H	H	—	O	81
9	$-CH_2CH=CH_2$	3-Cl	H	H	H	—	O	40
10	Pr	3-Cl	H	H	H	—	O	81
11	i-Pr	3-Cl	H	H	H	—	O	92
12	Me	3-Cl	H	H	5-Me	—	O	36
13	i-Pr	3-Cl	H	H	5-Me	—	O	49
14	Me	3-Cl	H	H	H	—	S	44
15	Et	3-Cl	H	H	H	—	S	30
16	i-Pr	3-Cl	H	H	H	—	S	44
17	Me	4-Cl	H	H	H	—	O	47
18	Et	4-Cl	H	H	H	—	O	52
19	i-Pr	4-Cl	H	H	H	—	O	69
20	Me	3-Br	H	H	H	—	O	72
21	i-Pr	3-Br	H	H	H	—	O	77
22	Me	3-F	H	H	H	—	O	76
23	i-Pr	3-F	H	H	H	—	O	71
24	Et	3-CF_3	H	H	H	—	O	81
25	i-Pr	3-CF_3	H	H	H	—	O	83
26	i-Pr	3-CF_3	H	H	H	O	O	34
27	Et	3-CF_3	H	H	H	—	S	65
28	Pr	H	H	Me	H	—	O	58
29	Et	3-Cl	4-Cl	H	H	—	O	34
30	i-Pr	3-Cl	4-Cl	H	H	—	O	42
31	Et	3-Cl	5-Cl	H	H	—	O	24
32	i-Pr	3-Cl	5-Cl	H	H	—	O	33
33	Me	3-NO_2	H	H	H	—	O	17
34	i-Pr	3-NO_2	H	H	H	—	O	56
35	Me	3-MeO	H	H	H	—	O	51
36	i-Pr	3-MeO	H	H	H	—	O	75
37	Me	3-Me	H	H	H	—	O	76
38	Et	3-Me	H	H	H	—	O	76
39[b]	i-Pr	3-Me	H	H	H	—	O	89
40	i-Pr	3-Me	H	H	H	O	O	42
41	Et	3-Et	H	H	H	—	O	66
42	i-Pr	3-Et	H	H	H	—	O	66
43	i-Pr	3-CF_3	4-Cl	H	H	—	O	10
44	Bu	3-CF_3	4-Cl	H	H	—	O	4
45	placebo							9
46	furosemide							82

[a] The dose was 100 mg/kg, p.o. administered to saline-loaded (25 ml/kg)rats. [b] Torasemide.

Table 2: Oral rat[a] diuretic activity of three selected 4-anilino-3-pyridine-sulfonylureas.



No.	R	R^1	Dose (mg/kg)	mEq × 100/kg/4 h			Na^+/K^+	$\frac{Na^+ + K^+}{Cl^-}$
				Na^+	K^+	Cl^-		
Control	—	—	0	40	64	56	0.625	1.86
8	Et	3—Cl	1.25	205	164	346	1.25	1.07
			2.5	402	212	594	1.90	1.03
			5	637	242	855	2.64	1.03
			10	687	251	928	2.73	1.01
38	Et	3-Me	1.25	301	188	445	1.60	1.10
			2.5	497	238	714	2.09	1.03
			5	663	256	914	2.58	1.00
			10	761	288	1029	2.64	1.02
39[b]	i-Pr	3-Me	1.25	371	268	546	1.79	1.06
			2.5	564	249	794	2.26	1.02
			5	690	248	909	2.74	1.02
			10	798	282	1067	2.83	1.01

[a] Saline-loaded (25 ml/kg) animals. [b] Torasemide.

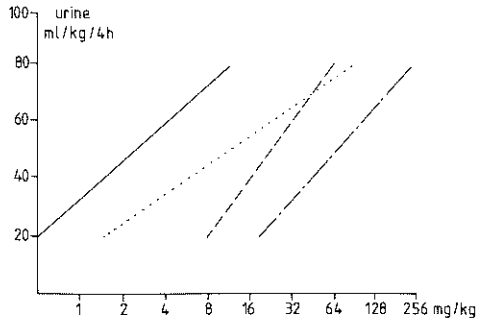


Fig. 4: Comparison of torasemide (——) with other diuretics piretanide (·····), furosemide (– – –) and bumetanide (— · — · —) in the oral rat test.

5. Overview on the pharmacological properties of torasemide in the rat

Because, in the tests presented so far we could establish that torasemide was the most active representative of this first series of sulfonylurea diuretics and also showed a steep linear dose response relationship like common loop diuretics, the pharmacological properties have been studied in rats more in detail.

5.1. Methods [14, 15]

The diuretic activity of torasemide was evaluated according to conventional methods. Male Sprague-Dawley (120—160 g) and Wistar (220—240 g) rats, with free access to food and water until the start of the experiment, were housed in metabolism cages in groups of 2 to 3 according to the body weight. At the time of dosing, the animals were orally loaded with 30 ml/kg of isotonic saline. Urine was collected for 4 h after i.v. or p.o. administration and assayed for volume, for sodium and potassium (flame emission), for calcium (atomic absorption) and for chloride and phosphate (colorimetry).

The urinary fractional excretion of water and electrolytes was studied in function of time in anesthetized Wistar rats with an average body weight of 381 g, using clearance determinations. Inulin clearance was used as measurement for glomerular filtration rate. Urinary fluid losses were quantitatively replaced by isotonic saline infused at a rate equal to the urinary flow.

Pharmacokinetics investigations were performed following oral and i.v. administration in male fasted Wistar rats with an average body weight of 150 g. Plasma concentrations of torasemide were determined using HPLC method (detection limit: 0.05 µg/ml).

The binding of torasemide to plasma proteins was determined by an ultrafiltration method after incubation of rat plasma in vitro at 37 °C during 1 h with different concentrations of ^{3}H-torasemide. The interaction of diuretics and cumarine derivative warfarin was studied in vitro with human serum. Protein binding was measured by equilibrium dialysis at 25 °C.

5.2. Results

5.2.1. Comparison of i.v. and oral application of torasemide

In a first series of experiments, i.v. and oral application of torasemide were compared. In male rats which were loaded with 30 ml 9‰ NaCl-solution/kg body weight increasing doses of torasemide orally (0.2—19.5 mg/kg) or intravenously (0.2—7.8 mg/kg) were given.

Fig. 5 summarizes the diuretic and saluretic effects. It is obvious, that the effects increased linearly with the log dose. The threshold dose was 0.2 or 0.5 mg/kg depending on the parameters measured. Above 7.8 mg/kg the effects tended to a ceiling value which was equal to the maximal excretion of water and sodium chloride that could be obtained with a diuretic treatment in our experimental conditions. The sodium/potassium excretion ratio greatly increased with dose. The results after i.v. administration were similar to those after oral administration, the curves were practically superposable. This was a clear advantage in comparison with other common diuretics.

Within these experiments the diuretic effect started approximately 15 min following the oral and 5 min following the i.v. administration of torasemide.

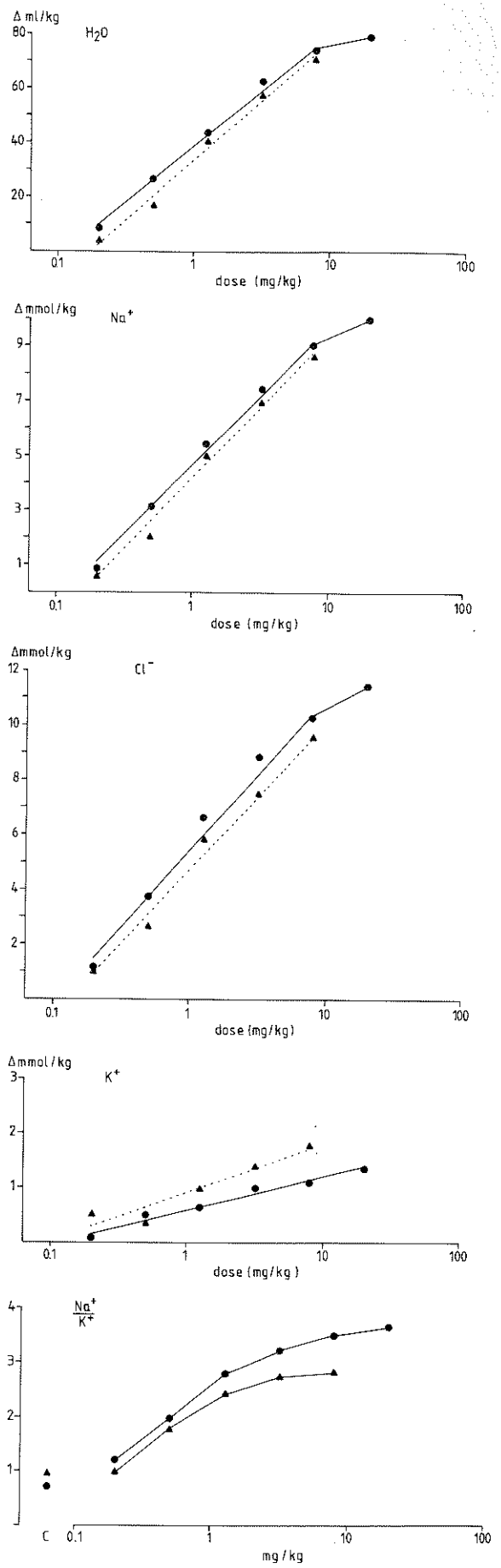


Fig. 5: Effects of torasemide on urinary volume, sodium, chloride and potassium excretion, and Na/K ratio after oral (●) and intravenous (▲) administration in rats (0—4 h collecting period). Each point represents the mean of 7 experiments. C = controls.

At all dose levels the diuretic effect, seen within 4 h, was mostly confined to the first 2 h. However, if the fluid and NaCl losses were replaced hourly by s.c. injection of isotonic NaCl solution, the diuretic action was still demonstrable after 8 h (Fig. 6).

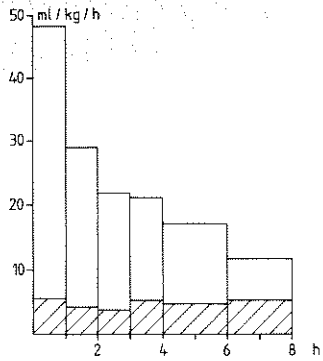


Fig. 6: Urinary flow (ml/kg/h) for an 8-h period following oral administration of 10 mg/kg in rats with hourly replacement of urinary losses by an equal volume of isotonic saline. □ Torasemide; ▨ controls.

5.2.2. Comparison of torasemide and furosemide

The results of a second series of experiments comparing torasemide (0.2 to 20 mg/kg p.o.) and furosemide (8 to 128 mg/kg p.o.) are shown in Fig. 7. A linear log dose-effect relationship was observed with both diuretics for the excretions of water, Na^+ and Cl^-. Torasemide was more potent than furosemide on a weight basis but because of the non-parallelism between both curves, the potency ratio, as far as water and Na^+ excretions were concerned, decreased from approximately 40 to 9 with increasing doses. The maximal effects obtained were similar for torasemide and furosemide. As far as K^+ was concerned, the difference was less pronounced, which means that for the same sodium excretion furosemide increased potassium excretion to a larger extent

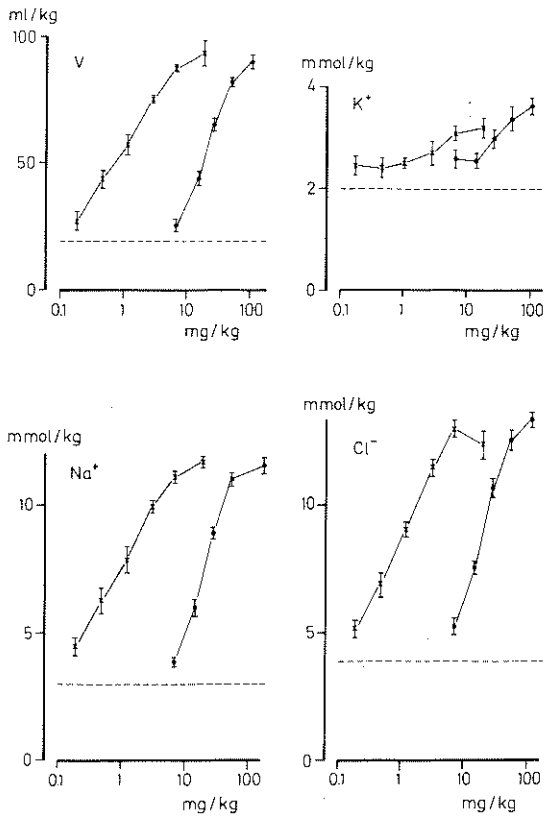


Fig. 7: Effect of torasemide (x) and furosemide (●) on urinary volume, and sodium, chloride and potassium excretion after oral administration in rats. Each point is the mean of 5 experiments.

than did torasemide. Both torasemide and furosemide increased Ca^{++} excretion dose-dependently and in a parallel way but torasemide was 35 times more potent and produced a 30 % higher ceiling value than furosemide ($p \leq 0.001$). Both drugs did not have any significant effect on inorganic phosphate excretion except at the highest doses. A weak but significant increase was observed from 0.35 mmol/kg in control rats to 0.61 mmol/kg after 20 mg/kg of torasemide ($p \leq 0.05$) and 128 mg/kg of furosemide ($p \leq 0.01$).

In a third series of experiments, the time course of diuretic and saluretic action of torasemide and furosemide after i.v. administration were compared. Fig. 8 shows the fractional water and electrolyte excretions in the urine after various i.v. doses of torasemide and furosemide as single bolus injections in rats. In this experiment, 2 mg of torasemide were approximately as potent as 10 mg furosemide regarding fractional water and sodium excretion. However, for the same natriuresis, furosemide produced a larger increase in kaliuresis than torasemide, the urinary Na/K ratios were higher after each dose of torasemide especially during the second hour of the experimental period.

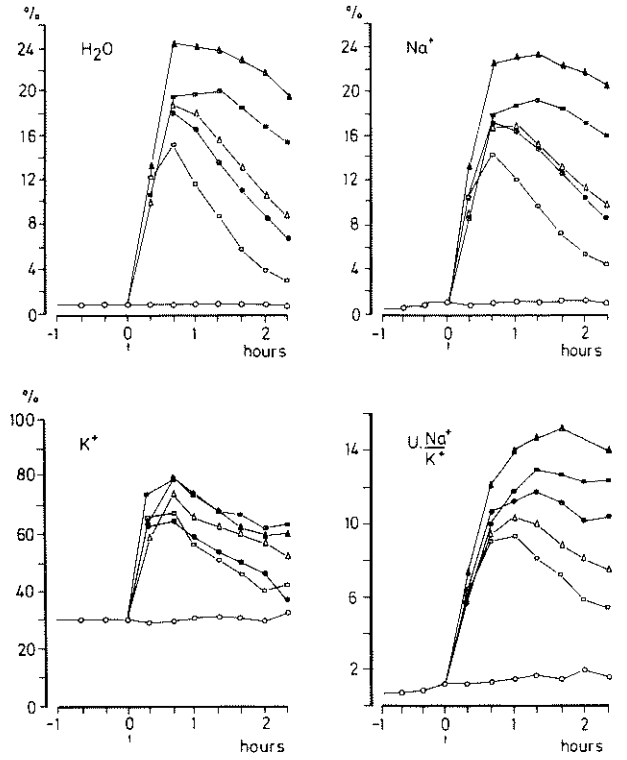


Fig. 8: Fractional excretion of water, sodium and potassium, and urinary Na/K ratio before and after administration of placebo (○), torasemide (2 mg/kg ■, 5 mg/kg ▲, 8 mg/kg ●) and furosemide (5 mg/kg □, 10 mg/kg △).

For both drugs, the onset of activity was rapidly reaching the maximal effect 20—40 min after dosing. Then a gradual decline could be observed, showing a trend to a longer duration of action with higher dose of torasemide. For example, torasemide given at doses of 2 and 5 mg/kg produced a similar peak sodium fractional excretion, but after 2 h the natriuretic response to 5 mg/kg was significantly higher ($p \leq 0.01$) compared to 2 mg/kg.

A maximum mean inhibition of the tubular reabsorption of sodium of 22 % also proved that torasemide is a "high ceiling" diuretic.

5.2.3. Pharmacokinetics of torasemide in the rat

Fig. 9 shows the plasma concentration versus time profiles of torasemide given intravenously and orally to rats (10 mg/kg). The intravenous data show a biexponential pattern allowing an analysis according to a 2-compartment open model [16]. The same model was applied to the oral administration curves.

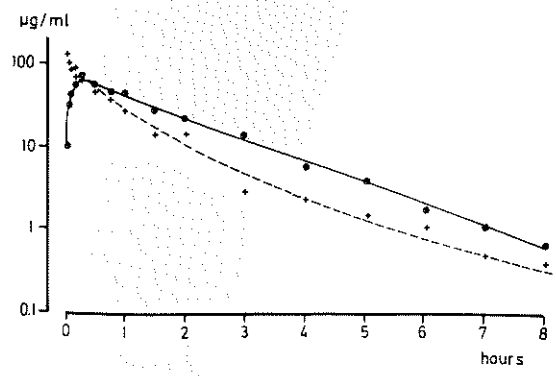


Fig. 9: Torasemide plasma concentrations in function of time after the administration of torasemide 10 mg/kg i.v. (+) or orally (●) to rats (n = 5 per group).

For the dose of 10 mg/kg of torasemide in the rat, the $t_{1/2}$ of the β-phase was 1.68 h after intravenous administration and 1.47 h after oral administration. The mean value of total apparent distribution volume was 251 ml/kg calculated for the intravenous route. Total body clearance was 103 ml/kg/h. For the dose of 1 mg/kg administered intravenously the values were 1.04 h ($t_{1/2}$ β), 126 ml/kg (V), and 83 ml/kg/h (total body clearance).

The pharmacokinetic data are given in Table 3. The bioavailability estimated on the basis of the ratio of the areas under the curve for oral and intravenous administration was calculated as 0.88 (1 mg/kg) and 1.24 (10 mg/kg) for the rat, and were in agreement with the similarity of the diuretic and saluretic dose-response curves after oral or intravenous administration.

Table 3: Pharmacokinetic parameters in the rat based on a 2-compartmental open model.

Parameters		Torasemide	
		1 mg/kg	10 mg/kg
i.v.			
α	(h^{-1})	3.39	1.22
β	(h^{-1})	0.66	0.41
A	(µg ml^{-1})	10.78	91.21
B	(µg ml^{-1})	5.83	9.13
$t_{1/2}$ β	(h)	1.04	1.68
K_{12}	(h^{-1})	1.05	0.11
K_{21}	(h^{-1})	1.62	0.49
K_{el}	(h^{-1})	1.39	1.04
V_C	(ml kg^{-1})	60.18	99.66
V_d	(ml kg^{-1})	125.9	251.0
AUC	(µg h ml^{-1})	12.14	94.10
CL.B	(ml h^{-1} kg^{-1})	83.51	103.49
p.o.			
K_a	(h^{-1})	10.70	10.89
$t_{1/2}$ β	(h)	1.94	1.47
AUC	(µg h ml^{-1})	10.63	128.19
Bioavailability	(%)	87.51	123.87

5.2.4. Plasma protein binding

With rat plasma the protein binding was 99.5 % for torasemide concentrations of 0.025 and 0.05 mg/ml. In the dog it was 98.4 % for concentrations of 0.005 and 0.020 mg/ml.

The extent of binding of some drugs can be influenced by the presence of other drugs and this can give rise to clinically important interactions. This is known especially for the interaction of diuretics and cumarin derivatives. Using human serum we therefore tested in vitro if there was an interaction of torasemide and the cumarin derivative warfarin. The results are given in Fig. 10 in comparison with phenylbutazone, for which a displacing effect on the warfarin binding has been described. Obviously the percentage free concentration of warfarin was not influenced by any concentration of torasemide up to 100 µg/ml in contrast to phenylbutazone. This might also be of clinical relevance especially because the therapeutic range of torasemide lies between 1—10 µg/ml.

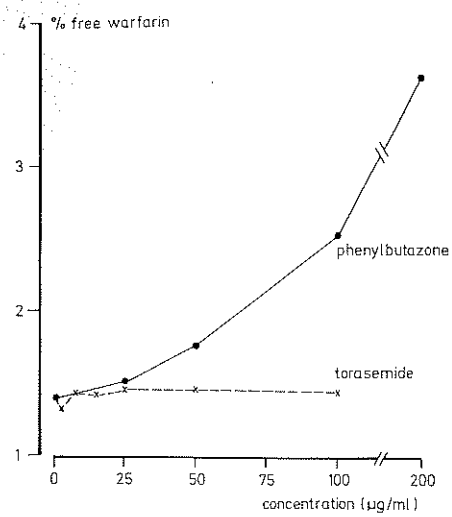


Fig. 10: Effect of different concentrations of torasemide or phenylbutazone on the percentage free warfarin (initial warfarin concentrations 2.56 µg/ml). Each point is the mean of 2 determinations.

6. Conclusion

Animal experiments show that torasemide is one of the most active derivatives of a new chemical class of diuretics, the 4-amino-3-pyridine-sulfonylureas. It is thus not chemically closely related to any of the known marketed diuretics. Its pharmacodynamic pattern of action in rats is qualitatively similar to that of other loop diuretics. But, the dose-response curve for equieffective saluresis for torasemide was lower and somewhat flatter than for furosemide. As a result there were differences in the potency of 1 : 9 (at high doses) to 1 : 40 (at low doses). Moreover, in comparison with furosemide torasemide displayed interesting advantages:

— equipotent activity after i.v. and oral application;
— almost 100 % bioavailability after oral administration;
— lower potassium excretion;
— longer duration of action.

These features may be promising for the clinical use of the drug.

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