would protect 50 per cent of the mice against 20,000,000 organisms. This infecting dose represents 100,000–1,000,000 LD_{50}.

Table 1 records the MEC and MED for the eight cultures, four of which were sensitive and four resistant according to *in vitro* tests. Strains 1, 2, 3, and 4 were isolated from patients before treatment with streptomycin and had never been exposed to this drug *in vitro*. These same strains, after acquiring varying degrees of resistance to streptomycin according to *in vitro* assay (1a in a patient and 2a, 3a, and 4a *in vitro*), required correspondingly higher MED in mice. In fact, we have not been able to demonstrate that it is possible to protect mice against strains capable of *in vitro* growth at 525 units/cc. and above. Strain 1b, produced by cultivating 1a in Levinthal broth in the absence of streptomycin, is shown to be sensitive *in vivo* and *in vitro*. It seems clear that high correlation exists between the MEC *in vitro* and the MED necessary to protect mice against 15,000,000–20,000,000 organisms under the circumstances of the experiments. The results indicate that the simple *in vitro* test recommended should suffice for assaying the sensitivity of strains from patients to be treated with streptomycin.

TABLE 1

RELATION BETWEEN MEC* ON LEVINTHAL AGAR AND MED† SUFFICIENT TO PROTECT MICE AGAINST 20,000,000 ORGANISMS PER MOUSE

Strain No.	Sensitive Strains MEC	Sensitive Strains MED	Resistant Strains MEC	Resistant Strains MED
1	1.1	39.0		
1a			525.0	> 630.0
1b	13.0	39.0		
2	1.6	19.5		
2a			73.0	315.0
3	1.1	19.5		
3a			> 525.0	> 1,575.0
4	0.8	19.5		
4a			1,078.0	> 1,575.0

* Minimum effective concentration *in vitro* units/cc. of culture media.
† Minimum effective dose units per mouse required for protection of 50 per cent of animals.

The results of earlier studies of the protective capacities of serum and sulfadiazine against lethal Type b *H. influenzae* infections in mice have been published (*1*). Experiments were designed to compare the protective power of streptomycin alone and in conjunction with sulfadiazine with that obtained by specific serum along with sulfadiazine. The results are tabulated along with those reported previously.

Protective Agent	*Maximum LD_{50} Protection*
Sulfadiazine	10,000
Specific rabbit serum	10,000–100,000
Sulfadiazine and serum	1,000,000
Streptomycin	100,000,000
Streptomycin and sulfadiazine	100,000,000

It is seen that the protective capacity of streptomycin alone equals that obtained by combining its action with sulfadiazine. This degree of protection by streptomycin was exhibited in four experiments in which two different strains of Type b *H. influenzae* were tested. Protection beyond 100,000,000 LD_{50} has not been explored, but the data show clearly that streptomycin alone is more effective against massive *H. influenzae* infections in mice than serum used in conjunction with sulfadiazine.

The foregoing observations have led us to treat 10 influenzal meningitis patients with streptomycin alone. The results, which will appear elsewhere, have been encouraging.

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Urinary Recovery of Penicillin After Oral Administration With Antacids and Buffers

MILTON J. GOLDEN and FRANZ M. NEUMEIER

Research Laboratories, McKesson & Robbins, Inc. Bridgeport, Connecticut

The importance of neutralizing gastric acidity for the therapeutic success of orally administered penicillin has been unquestionably established (*1*). Early studies on penicillin absorption and excretion have proved that most of the orally administered penicillin is destroyed by stomach acidity (*1, 9*). The presence of small amounts of penicillin in the urine and in the blood after oral administration indicated a partial penicillin absorption from the intestines; moreover, a corresponding increase in both urine and blood penicillin levels has been produced by the oral administration of larger doses of this antibiotic (*9*).

These observations suggested that oral therapy of penicillin is possible, once sufficient penicillin intake has been assured and its destruction by gastric acidity eliminated. The extent to which the gastric acidity is neutralized determines the efficacy of using a particular buffer or antacid for the absorption of penicillin. Several antacids (*10*), buffers (*10*), and oils (*4, 6*) in fluid form or in gelatin capsules have been used to fulfill this purpose. The results reported in the literature are somewhat confusing and conflicting (*2, 3, 5, 8*). In most instances the investigations were carried out by comparing the responses of sev-

eral individuals, and the results of penicillin concentration in both urine and blood have been shown to vary considerably (*3*).

To compare the effectiveness of buffers and antacids by their known ability to neutralize gastric acidity, and to prevent individual variations, we found it

TABLE 1

THE BUFFERS AND ANTACIDS STUDIED WITH THEIR DOSAGES

Buffer or antacid	Quantity taken orally in 200 cc. of water
Sodium citrate U.S.P.	2 grams
Cottonseed oil in gelatin capsule	1 cc.
Aluminum gel*	8 cc.
Aluminum hydroxide gel*	7½ cc.
Sodium bicarbonate U.S.P.	2 grams
Calcium carbonate U.S.P.	2 grams
Sodium chloride U.S.P.	1.7 grams
Antacid powders containing a mixture of sodium bicarbonate, colloidal kaolin, magnesium trisilicate, and bismuth subcarbonate	2 grams

* Two different brands.

necessary to use only one normal individual (male) in our series of investigations. Some of the tests were repeated on other persons to check the findings.

The purpose of this report is to indicate the results of a study of the value of various buffers and antacids recommended for the oral administration of penicillin by the determination of the quantity of penicillin excreted in the urine over a period of six hours. In a future report these findings will be supplemented with blood penicillin levels, using the same antacids and buffers.

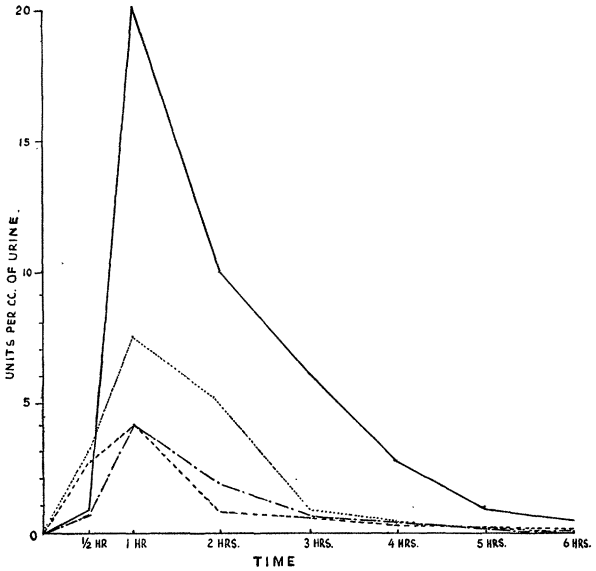

FIG. 1

——— Sodium bicarbonate
- - - - - - - - - - - Sodium chloride
——·——·—— Sodium phosphate (dibasic)
. . . . . Sodium-citrate

Table 1 lists the dosages of the buffers and antacids under study.

In each instance, 25,000 units of sodium penicillin dissolved in the aqueous solution or suspension of the buffer or antacid were taken by mouth approximately two hours after breakfast. The subject under study was instructed to abstain from food and liquids for at least two hours. To avoid any interference with subsequent doses of penicillin, the above buffers and antacids were distributed over a period of several months, so that only one of the compounds was taken either once a week or every other week.

Urine was voided after one-half hour and thereafter at hourly intervals for six hours. The volume of urine was measured and the samples kept in glass-stoppered bottles at a temperature of 3° C. until assayed. Since detectable quantities of penicillin were rarely found in the urine after the sixth hour, no assays were done after that period.

Penicillin was assayed by the Food and Drug Administration cylinder-plate method as of January 1945, using *Staphylococcus aureus* 209 and comparing the unknown samples with a standard penicillin curve prepared daily.

The urinary excretion of penicillin obtained with the various buffers and antacids is shown in Figs. 1 and 2.

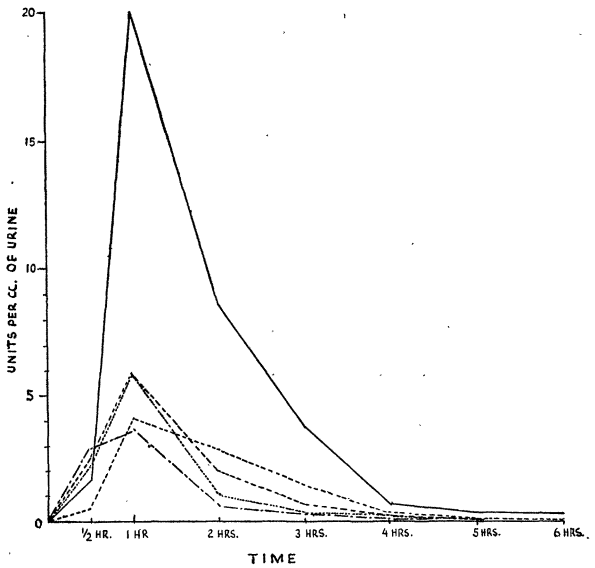

FIG. 2

——— Antacids containing sodium bicarbonate, colloidal kaolin, magnesium trisilicate, and bismuth subcarbonate
- - - - - - - - - - - *Aluminum gel
- - - - - - - - - - - *Aluminum hydroxide gel
——·——·—— Calcium carbonate
. . . . . Cottonseed oil

*Two different brands.

The penicillin potency expressed in Oxford units

per cubic centimeter of urine is plotted against time, and the one-half-hour sample includes the volume of urine present in the bladder prior to the test. The value given for each point on the graph is the average of two determinations. Physiological saline has been used as a control, and the urinary excretion of penicillin confirms the statement that penicillin administered without buffer or antacid is absorbed to a slight extent (*9*).

When penicillin is combined with an antacid powder containing a mixture of sodium bicarbonate, colloidal kaolin, magnesium trisilicate, and bismuth subcarbonate, or sodium bicarbonate alone, the urinary excretion of penicillin surpasses that observed by any substance of the group studied. We have been able to obtain reproducible urinary penicillin excretion curves, when a combination with the antacid powder mixture was used. The same results have been found not only on the subject under study but also on several other male individuals.

Table 2 summarizes the total percentage recovery of penicillin in the urine after six hours by multiplying the values of the unit potency per cubic centimeter of urine by the volume of urine. From these values it is again apparent that the maximum excretion occurs when antacid combinations or sodium bicarbonate alone have been used.

TABLE 2

PERCENTAGE RECOVERY OF PENICILLIN IN URINE

Material administered	Per cent	Units
Aluminum gel	2.0	500
Aluminum hydroxide gel	2.6	650
Calcium carbonate U.S.P.	2.6	650
Sodium phosphate (dibasic)	3.20	800
Cottonseed oil in gelatin capsule	2.5	625
Sodium chloride U.S.P.	1.9	475
Sodium citrate U.S.P.	5.0	1,250
Sodium bicarbonate U.S.P.	8.7	2,175
Antacid powders containing sodium bicarbonate, colloidal kaolin, magnesium trisilicate, and bismuth subcarbonate	9.0	2,250

Therapeutically, the use of sodium bicarbonate has its limitations, due to the danger of alkalosis. However, with antacids containing several buffers and smaller amounts of sodium bicarbonate, no apparent change in the urinary hydrogen-ion concentration has been observed.

Antacid powders used in combination with penicillin produced a unit potency of penicillin excretion of 20 Oxford units/cc. of urine within the first hour (Fig. 2), whereas the maximum for aluminum hydroxide gel was 4–6 units/cc. and for sodium citrate, 7.5 units/cc. Furthermore, the total penicillin recovery after oral administration with antacid powders exceeds that observed with any of the group studied.

The penicillin values obtained from the urinary excretion do not necessarily infer a corresponding blood level. It is merely suggested that this may be the case.

The necessity of restricting our investigations to males became evident when it was found impossible to obtain reproducible characteristic penicillin urinary excretion with the females studied. Similar findings in females have also been reported by Perlstein, *et al.* (*8*), who found an unexplainable maximum excretion in the eighth hour. The mechanism of urinary clearance would seem to vary in males and females. A similar difference in kidney physiology between males and females has been reported by Smith (*11*). Moreover, Oster (*7*) has recently found a histochemical difference in the kidneys of male and female rats.

Summary. Combinations of sodium bicarbonate, colloidal kaolin, magnesium trisilicate, and bismuth subcarbonate with penicillin produce a higher penicillin titer in the urine than the various antacids and buffers recommended for oral penicillin therapy.

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Transmission of *Salmonella enteritidis* by *Pulex irritans* and *Ctenocephalus canis*

GERARDO VARELA

Instituto de Salubridad y Enfermedades Tropicales

and

J. OLARTE

Escuela Nacional de Ciencias Biológicas

Mexico, D.F.

The possibility of transmitting an infection by means of *Pediculis vestimenti* as a host of *Salmonella enteritidis* has been studied by Huang and Lien (*1*).

Later, Steinhaus (*3*) isolated the following Salmonelleae from insects: *Eberthella pyogenes* from *Neobius fasciatus* var. *fasciatus* and *Eberthella insecticola* from *Conocephalus fasciatus* var. *fasciatus, Oncopeltus fasciatus,* and *Loxa variegata.*

More recently, Parker and Steinhaus (*2*) proved