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Soap Bacteriostats

ERIC JUNGERMANN, Armour Grocery Products Comany, Chicago, Illinois 60680

Abstract

The growing use of bacteriostats in soaps and the various methods for screening these compounds are reviewed critically. Discussed are (1) in vitro techniques to establish antibacterial activity, substantivity tests using skin disk, fingerprint, or radioactive tracer techniques, and microbiological availability determinations; (2) safety testing procedures; (3) in vivo tests to determine deodorancy and degerming efficiency. Performance in clinical trials, designed to evaluate the contribution of bacteriostatic soaps to the treatment of bacterially caused infections, is examined. Discussed are studies on the control of erythrasma, acne, diaper rash, and secondary cutaneous infections.

These techniques are illustrated by comparing two bacteriostatic systems, A and B, in soaps. System A contains 0.75% TCC and 0.75% hexachlorophene; System B contains 0.67% TBS, 0.67% TCC, and 0.67% Irgasan CF_3. The data showed excellent correlation between in vitro screening techniques and actual in vivo performance characteristics.

Introduction

ANTIBACTERIAL AGENTS have been used in soaps for some time. Prior to World War II the most widely used materials were certain cresol derivatives. These tended to impart a strong characteristic odor to soaps, which limited their use in the consumer toilet soap market. In 1941 Kunz and Gump (1) discovered that certain halogenated bisphenols maintained their antibacterial activity in the presence of soap without imparting negative qualities. The most promising of these materials was hexachlorophene [(2,2'-methylenebis) (3,4,6-trichlorophenol)] which subsequently found wide usage in toilet soaps.

Though there has been a high level of research activity since 1950 to discover new soap bacteriostats, the number of materials which were developed and which were found suitable from a technical, safety, and economic point of view is small. The reason for this becomes apparent when one considers all the properties that a bacteriostat must possess to become a successful candidate for use in toilet soap. Some of these are listed below: 1) broad spectrum antibacterial activity in the presence of soap; 2) skin substantivity; 3) effective deodorancy; 4) efficacy in skin degerming and in the control of certain bacterially caused skin conditions, such as diaper rash, erythrasma, and secondary infections of cuts, scratches, and abrasions; 5) chemical stability in soap; 6) compatibility with color and odor of finished products; 7) nonreactivity with other components in the soap, i.e., perfumes, antioxidants, brighteners, etc.; 8) mildness and safety for general use of the finished product; and 9) satisfactory economics.

Relatively few compounds have been found to meet all these requirements. The most important presently in use are, hexachlorophene (2,2'-methylenebis [3,4,6-trichlorophenol]) 3,4,4'-trichlorocarbanilide (TCC), 3,4',5-tribromosalicylanilide (TBS), and 4,4'-dichloro-3'-(trifluoromethyl) carbanilide (Irgasan CF_3 from Geigy Chemical Corporation, Ardsley, N.Y.). These compounds have, in general, excellent properties and are widely used though there can be certain drawbacks. Thus the substituted ureas can cause processing problems because of some chemical instability in alkali media at elevated temperatures; bisphenols tend to be slightly light-sensitive; in the case of the halogenated salicylanilides, despite impressive mildness data on soaps containing these materials which

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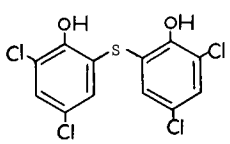
have been obtained in standard toxicological tests and human studies, instances of isolated cases of photodermatitis attributed to such soaps have been reported and are perhaps being misconstrued as being more widespread than the facts indicate (2).

Many other chemicals have been reported effective as soap bacteriostats. The most important of these are shown in Fig. 1 and include bithionol [2,2′-thiobis (4,6-dichlorophenol)] and 3,3′,4′,5-tetrachlorosalicylanilide, both of which have been identified as photosensitizers (3–5); tetramethylthiuram disulfide; 3,5-dibromo-3′-trifluoromethyl salicylanilide; and zinc 2-mercaptopyridine-1-oxide.

Perhaps the most significant advance in soap bacteriostats in the last 10 years has been the development of synergistic soap-active bacteriostatic systems. The term "synergistic activity," as used in this paper, means an antibacterial effect which is greater in combination than the sum of the antibacterial effects of the separate components. Casely et al. (6,7) developed synergistic binary systems comprised of mixtures of the isomeric trihalogenated carbanilides (3,4,4′- and 3,3′,4-) with a number of halogenated bisphenols and alkylated halogenated bisphenols and, similarly, between some halogenated salicylanilides and halogenated bisphenols. An example of such "synergistic activity" is shown in Table I (8) and is discussed in detail by Noel et al. (9).

Subsequent patents issued in this area claim synergistic activity in soap for various combinations of commercially available chemicals in binary and ternary systems. Systems for which synergism is claimed include various combinations of halogenated bisphenols, trichlorocarbanilides, 4,4′-dichloro-3-(trifluoromethyl) carbanilide, brominated salicylanilides, and 2-mercaptopyridine-1-oxide and its salts (10–15). The principle of synergism has been commercially used by several soap manufacturers.

This paper is concerned with the question of evaluation and selection of bacteriostatic agents for use in soaps. It covers both the in vitro and in vivo testing required to establish performance criteria aimed at maximizing antibacterial and deodorancy effectiveness.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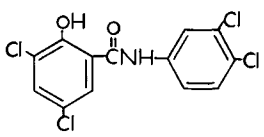
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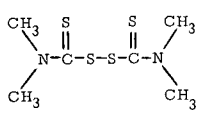
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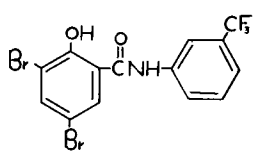
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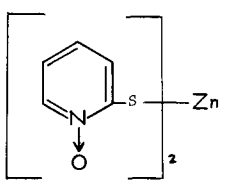
Zinc 2-mercaptopyridine -1-oxide

FIG. 1. Additional soap-active bacteriostats.

TABLE I

Antibacterial Effectiveness of Varied Ratios of Hexachlorophene and 3,4,4′-Trichlorocarbanilide (TCC) in Soap (Modified Agar Streak Method)

Ratio	Bacterial Growth Ratings[a] Total antibacterial agent at 0.04 ppm	at 0.02 ppm
100% Hexachlorophene, 0% TCC	2	3
90% Hexachlorophene, 10% TCC	0	2
70% Hexachlorophene, 30% TCC	0	2
50% Hexachlorophene, 50% TCC	0	1
40% Hexachlorophene, 60% TCC	1	2
30% Hexachlorophene, 70% TCC	1	3
20% Hexachlorophene, 80% TCC	1	3
10% Hexachlorophene, 90% TCC	2	3
0% Hexachlorophene, 100% TCC	3	3

[a] 0, no growth; 1, slight growth; 2, moderate growth; 3, heavy growth.

Screening of Soap Bacteriostats

Screening for soap bacteriostats involves extensive in vitro, safety, and in vivo tests. The in vitro tests include 1) the determination of antibacterial activity, per se, as well as in soap; 2) substantivity tests to determine whether the soap bacteriostats are held on the skin; 3) determination of microbiological availability, a property which evaluates the combined effect of inherent bacteriological activity and skin substantivity.

Safety tests include the standard types of toxicological studies summarized in Table II. These involve studies on the bacteriostatic system itself, as well as the system in soap, and include skin and eye irritation, acute oral and dermal toxicity, subacute dermal toxicity, skin sensitization, and photosensitization. Specialized tests, such as teratogenicity, skin absorption, and others are occasionally run, particularly when antibacterial claims are made for the soap.

In vivo tests are designed to evaluate the usefulness of the antibacterial agents in deodorancy effectiveness, the reduction of cutaneous bacterial populations, and performance in various clinical studies aimed at controlling diaper rash, erythrasma, secondary skin infections, and other dermatologic conditions.

The various in vitro and in vivo techniques will be described in some detail by using two synergistic bacteriostatic systems, A and B, for comparison purposes. System A is a soap containing a mixture of 0.75% hexachlorophene and 0.75% TCC; System B is a soap containing a mixture of 0.67% TCC, 0.67% TBS, and 0.67% Irgasan CF_3.

Experimental Procedures and Data

In Vitro Testing

Antibacterial Activity. Several routine bacteriological techniques are used to determine the antibacterial activity of soap bacteriostats in the presence of soap against test organisms. They include agar streak dilution tests (8), tube dilution tests (16), and zones of inhibition (17). In these tests a medium

TABLE II

Some Toxicological Studies Employed to Determine Product Safety

Tests	Species
Acute oral toxicity (LD 50)	Rats and dogs
Acute dermal toxicity (LD 50)	Albino rabbits
Eye irritation	Albino rabbits
Skin irritation	Albino rabbits
Skin sensitization	Guinea pigs
Subacute dermal toxicity tests	Albino rabbits
Repeat-insult patch test	Human beings
Photosensitization	Human beings and guinea pigs

TABLE III
Minimum Inhibitory Concentrations of Soaps Against Pathogenic Staphylococci and Streptococci

Organism[a]	M.I.C. (ppm) basis Total product	
	A	B
Staphylococcus PS 187	4	5
Staphylococcus S A 9 Smith (diffuse)	3	>4
Staphylococcus PS 42D	3	5
Staphylococcus Cowan I NCTC 8530	3	5
Staphylococcus Cowan II NCTC 8531	2–3	4
Staphylococcus Wood 46	2–3	4
Streptococcus Group A GS 208–4	2	4
Streptococcus Group A SS 510	3	6
Streptococcus Group B B1	3	5
Streptococcus Group B B5	6	10
Streptococcus alpha Group D DS 1455–65	9	>12
Streptococcus Group G DS 1426–65	2	5

[a] Dilution of culture, 1×10^{-2}.

is used which supports the growth of test organisms and does not neutralize the effect of bacteriostats. The organisms are bacteria of particular interest in skin infections, cross-infection, and body odor formation.

The data obtained in the screening of soaps which contain bacteriostatic Systems A and B have been reported in detail by the author (18). Results obtained against 26 strains of bacteria are shown in Tables III, IV, and V. In these tests System A consistently demonstrated a slight edge over System B with regard to antibacterial efficiency. As can be seen from the data, this superiority extended over a wide range of organisms and does not represent specially selected organisms.

Substantivity Tests

Three different procedures are used for evaluating the substantivity of bacteriostats: the Vinson (19) calfskin disk test, a fingerprint test (19), and radioactive tracer techniques (20).

The first two tests use 8% soap solutions, and results are evaluated by the appearance of zones of inhibition. In the Vinson calfskin test, the disk is soaked for 15 min, rinsed, and placed in a nutrient agar seeded with *Staphylococcus aureus* ATCC 6538. In the fingerprint test, the finger tips are soaked for several minutes, rinsed, and then pressed on seeded agar. Substantivity is based on zone ratings produced by these tests. Results obtained from these tests are shown in Table VI. As the data indicate, with these procedures, the two bacteriostatic systems, A and B, are essentially equivalent.

Tests based on zones of inhibition can be misleading. Extremely substantive materials have been found which yield small zones of inhibition; these materials are sometimes not readily removed either from calfskin or human skin and hence do not diffuse well into the agar medium. Typical examples of chemicals which fall into this category are cationic bacteriostats.

Radioactive tracer techniques provide more precise measurements of the substantivity of soap bacteriostats. The Armour laboratory recently concluded an extensive study comparing the relative substantivity of a number of compounds. Single materials, as well as the synergistic combinations represented by Systems A and B, were tested (20). In this study, hexachlorophene was tagged at the methylene bridge; TBS, TCC, and Irgasan CF_3 were tagged at the carbonyl group. Readings obtained immediately after application to human skin, as well as after 24 hr, are summarized in Table VII. As can be seen, the retention of System A (0.75% TCC and 0.75% hexachlorophene) was nearly four times that of System B (0.67% TBS, 0.67% TCC, and 0.67% Irgasan CF_3) immediately after application and nearly seven times greater after 24 hr.

TABLE IV
Minimum Inhibitory Concentrations of Soaps Against Types of Bacteria Responsible for Human Body Odor[a]

Organism[b]	M.I.C. (ppm) basis total product	
	A	B
Staphylococcus epidermis ATCC 155	4	6
Corynebacterium pseudodiphtheriticum ATCC 10700	3	5

[a] Cf. J. Meyer-Rohn, Fette Seifen Anstrichmittel *67*, 353 (1965).
[b] Dilution of culture, 1×10^{0}.

TABLE V
Minimum Inhibitory Concentrations of Soaps Against Miscellaneous Bacteria

Organism	Dilution of culture	M.I.C. (ppm) basis Total product	
		A	B
Sarcina lutea ATCC 9341	1×10^{0}	5	7
Sarcina lutea ATCC 9341A (streptomycin-resistant)	1×10^{0}	6	10
Corynebacterium hoagii F-17[a]	1×10^{-3}	7	10–20
Staphylococcus citreus W-10[a]	1×10^{0}	3	>5
Staphylococcus lysodeikticus W-13[a]	1×10^{-2}	3	>5
Staphylococcus W-5[a]	1×10^{-3}	5	6
Staphylococcus W-11[a]	1×10^{-1}	3	4
Staphylococcus W-14[a]	1×10^{0}	4	6
Bacillus subtilis ATCC 6460	1×10^{0}	5	7
Bacillus cereus ATCC 9592	1×10^{0}	5	7
Bacillus subtilis[b]	1×10^{0}	3	5
Brevibacterium ammoniagenes ATCC 6871	1×10^{0}	1	2

[a] Obtained from F. B. Engley, Department of Microbiology, University of Missouri.
[b] Obtained from Industrial Bio-Test Laboratories, Northbrook, Ill.

Microbiological Availability

Taber et al. (21) recently reported on the concept of "microbiological availability" for the evaluation of bacteriostatic agents in soap. This new approach describes the interaction of inherent bacteriostatic effectiveness with the quantity of material deposited on certain substrates. Use of the term "microbiological availability" rather than "substantivity" is not only more descriptive of the actual experimental event but defines more clearly the one characteristic of real importance in the evaluation of soap bacteriostats. In this test, calfskin or other proteinaceous materials are treated with either control or bacteriostatic soap solutions, rinsed, and inoculated with agar seeded with *S. aureus* ATCC 6538. Percentage reductions after specific periods of exposure to the soap solutions are determined by comparing the number of bacteria growing after treatment of a disk of the substrate with an Ivory (Procter & Gamble) soap solution, to the bacterial count after a similar treatment with the medicated soap. In the case of an effective bacteriostatic system, bacterial growth will be reduced rapidly and markedly.

Results obtained by utilizing the microbiological availability test are summarized in Fig. 2. Data are presented as percentage decreases in bacterial popula-

TABLE VI
Agar Plate Substantivity Tests on Antibacterial Systems A and B

Type of test	Rating	
	System A	System B
Skin disk test	4-excellent	3–4-good to excellent
Finger imprint test	3-good	3-good

TABLE VII

Retention of Radiotagged Bacteriostatic Systems after Application to Human Skin from Soap Solutions

	System A	System B
Applied to subject	0.678[a] μc	0.678 μc
Count after application	0.0272 μc/cm²	0.0075 μc/cm²
Count after 24 hr	0.0127 μc/cm²	0.0019 μc/cm²

[a] Corrected to same application level as System B.

tion on calfskin substrates. As can be seen, hexachlorophene and TBS, which have higher minimum inhibitory concentrations (MIC) than TCC (Table VIII), nevertheless are shown to be more inhibiting than TCC by this technique. Irgasan CF_3, a product with a much lower MIC than hexachlorophene, is, at best, equivalent in this test. These findings are explained by considering the interaction of inherent effectiveness and substantivity of the bacteriostats rather than either of these factors alone. A balance of each of these properties is required to achieve maximum effectiveness of a bacteriostatic system.

In a comparison of System A with System B it is found that System A is markedly superior in this test (Fig. 2). These results are in agreement with those obtained in the radioactive tracer studies (Table VII). The method has been extended to the use of a number of different strains of microorganisms, and these findings will be the subject of a subsequent publication.

In Vivo Testing

In vivo testing of bacteriostatic soaps falls into four major categories. These include: mildness tests, deodorancy tests, skin degerming tests, and clinical tests.

Mildness. Several methods for testing mildness have been reported in the literature. Kooyman and Snyder used patch tests and arm immersion procedures (22). These techniques magnify the effect of soap solutions on the skin and demonstrate differences in relatively short periods of time. Other types of patch tests have also been reported by Schwartz (23) and by Draize (24). More recently, a paper was published on the comparative mildness of an antibacterial soap containing 0.75% TCC and 0.75% hexachlorophene (Dial from Armour & Company) and a nonmedicated soap (Ivory) (25). This study was carried out at a hospital; 101 babies up to the age of 14 months served as subjects. The test was conducted over a period of 8 weeks under the supervision of a dermatologist. No evidence of irritation, contact allergies, or sensitization from either soap was observed during the test period. Results showed that the two soaps are of equivalent mildness.

Deodorancy. Deodorant efficiency is probably the most important property of antibacterial soaps from the consumer's point of view. Several comparative evaluation techniques have been reported, usually based on panel responses (8,47). Axillary odor development is either evaluated by the panelists themselves, by judges, or by both panelists and judges, and the data obtained are analyzed statistically. Because of the nature of these tests, there are many variables which must be taken into account in setting up a proper experimental design. Typical variables to be considered are whether the soaps are used in the right or left axilla, the season of the year, and the olfactory acuity of the panelists.

TABLE VIII

Inherent Effectiveness of Soap Bacteriostats Against *Staphylococcus aureus* ATCC 6538[20]

Name	Minimum inhibitory concentration ppm of Soap[a]
Hexachlorophene	30
3,4,4'-trichlorocarbanilide	20
3,4',5-tribromosalicylanilide	60
4,4'-dichloro-3-(trifluoromethyl) carbanilide	7

[a] Soap contained 1% by weight of bacteriostat.

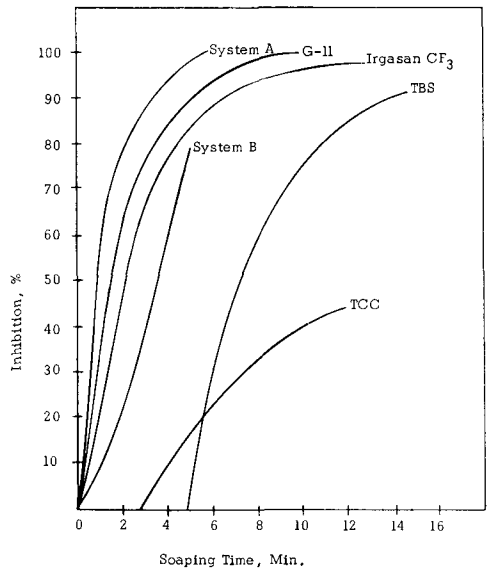

FIG. 2. Microbiological availability of soap germicides (*S. aureus* ATCC 6538). Individual chemicals tested at 1.0% in soap.

Results which were obtained in a comparison of the deodorancy efficiency of System A with System B, System A with a soap containing 0.75% TBS (Soap C), and System A with a nonmedicated (placebo) soap (Soap D) are shown in Fig. 3. The soap containing System A was found superior over Soap C and Soap D; there was no statistically significant difference between Systems A and B.

A newer technique for evaluating the deodorant efficacy of soaps has recently been reported by Dravnieks et al. (26–28). These investigators combined a novel sampling technique with gas-chromatographic detecting procedures. By sweeping the axillary areas with a stream of helium, collecting the volatiles, and passing the condensed materials through a GLC column after removing water, typical chroma-

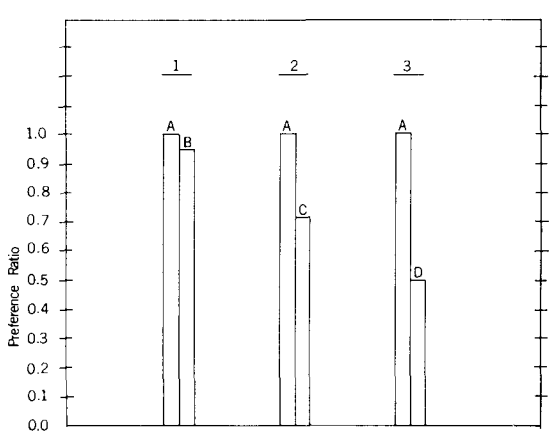

FIG. 3. Deodorancy evaluations. Preference ratio: 1) Soap A to soap B; 2) soap A to soap C; 3) soap A to soap D. Soap A contains 0.75% hexachlorophene and 0.75% TTC; soap B, 0.67% TCC, 0.67% TBS, and 0.67% Irgasan CF_3; soap C, 0.75% TBS; and soap D is nonmedicated.

TABLE IX
Some Differences Between Standard Hand-Degerming Tests

Test	Duration	Number of basins	Basins sampled
Price	2–4 weeks	10–14	1–14
Cade	2 weeks	5	1,4,5
Quinn	5 days	1 for each hand	1

tographic patterns were obtained. These were related to human body odors, as perceived olfactorily. Specifically designed equipment was utilized for collecting and handling these volatile materials and is fully described in the papers. Psychophysical scaling of odor-relevant GLC peaks was accomplished by splitting the helium stream between the detector and a "sniff" port so that an experienced observer could rate the character and intensity of odors corresponding to each peak in the "odorgrams." A technique for handling the data was derived which showed that the intensity of odor-relevant peaks was reduced by a factor of two to three when certain medicated soaps were compared to a nonmedicated soap.

Skin Degerming. The performance of an antibacterial soap, whether used for deodorant or for therapeutic purposes, is dependent upon its ability to degerm the skin. A particularly provocative methodological problem relates to evaluating reliably the efficacy of soaps in degerming the skin. Traditionally this has involved counting bacteria which are removed when the hands are washed under standardized conditions. Although many procedures have been tried, the most widely used are attributed to Price (29), Cade (30), and Quinn et al. (31). Modifications of the Price and the Cade tests have been described by Roman et al. (32), and by Kooistra et al. (33). A modification of the Quinn test was reported by Brown et al. (34). The Price technique gives an estimate of the total number of bacteria in the hands; the Cade test gives a measure of the bacterial population removed from the inner portion of the stratum corneum layer of the skin; and the Quinn method determines the bacteria in the outermost part of the skin including both transient and resident bacteria.

Significant differences exist between these procedures, and these can influence the data. In the Price and Cade procedures it is assumed that the number of bacteria in the hands would have remained constant if a nonmedicated rather than an antibacterial soap had been used during the entire test period. The Quinn test makes no such assumption but measures the effect of using an antibacterial product on one hand while the other is washed with the placebo.

The importance of determining the effect of an antibacterial soap on the bacteria found in the outermost part of the skin may be realized when it is considered that two of the chief vectors of hospital infection are the transfer of pathogens from the hands of the nurse or of the surgeon to the patient (35,36). For this reason the Quinn test is preferred as a means of measuring the practical effectiveness of such soaps. Complete details of these degerming tests may be found in the references. Table IX summarizes some of the differences between these test procedures.

Soap containing bacteriostatic System A was compared with soap containing bacteriostatic System B by using some of these degerming procedures. A modified Quinn test showed System A and System B equivalent in their ability to degerm the skin (34). A second study, by utilizing a modified Price procedure, reported no essential difference in the skin-degerming properties of System A and System B (37).

In a simulated surgical scrub degerming evaluation of soaps containing System A, System B, and Ivory soap, Litsky and Litsky (38) found no significant difference in the relative level of bacterial accumulation in surgical gloves worn for a period of one hour after pretreatment of the hands and forearms with the two soaps containing bacteriostatic agents. However a significantly greater bacterial accumulation was found in surgical gloves when the pretreatment was carried out with Ivory soap.

Clinical Tests. Having established safety, mildness, deodorancy, and skin-degerming effectiveness, the final step in the evaluation of an antibacterial soap is to determine its efficacy in contributing to the control of certain bacterially caused skin disorders and in the control or prevention of secondary infections. This is done in statistically designed and carefully controlled clinical trials. A number of specific studies have been carried out with medicated soaps in the treatment of diaper rash, erythrasma, and secondary infections in cuts, scratches, and abrasions. Typical examples of some clinical studies reported in the literature and the results obtained are listed in Table X (40–46,48).

Clinical studies evaluating the use of antibacterial soaps in secondary cutaneous infections require the use of large numbers of subjects drawn, preferably, from prisons, detention homes, or military barracks where the daily life is regimented and subjects are available to the clinical investigator at nearly all times. Two studies have been reported in the literature in which medicated soaps, represented by System A or System B, were compared against a placebo soap

TABLE X
Clinical Results Obtained on Using Antibacterial Soaps in Various Skin Conditions

Type of study	Soaps used	Results	References
Secondary Cutaneous Infections	Soap A[a] vs. placebo	Soap A significantly better	40,48
	Soap B[a] vs. placebo	Soap B significantly better	41
	Soap A vs. Soap B	Soap A significantly better than Soap B	42
Diaper rash	Soap A vs. placebo	Soap A significantly better	43
Erythrasma	Soap A vs. placebo	Soap A significantly better	44
	Soap B vs. placebo	Soap B significantly better	45
Acne	Soap A vs. Soap B	Soap A and Soap B are equivalent	46

[a] Soap A contains .75% TCC and .75% hexachlorophene; Soap B contains .67% TCC, .67% Irgasan CF3, .67% TBS.

under highly controlled conditions (40,41,48). In these cases the medicated soaps proved significantly better in the prevention of superficial cutaneous infections. In a more recent study Dubow (42) compared System A directly with System B and found a marked superiority of System A over System B.

Similarly, studies on erythrasma may be satisfactorily conducted in similar environments by using smaller panels of afflicted subjects drawn from large populations. Both System A and System B have been tested for efficacy in reducing erythrasma, and both were found effective in this application (44,45).

Diaper-rash studies employ hospital nursery panels, which are subsequently followed into the home environment for as long as the test requires. Soap containing System A was found effective in several studies (43).

In addition to the studies listed in Table X, Osbourn et al. have found a soap containing System A effective in the treatment of tropical ulcers (39).

The results of these clinical studies provide good confirmation of the findings of the preliminary in vitro and degerming tests described in this paper.

Comments

Deodorant and antibacterial soaps have represented the most rapidly growing segment of the toilet soap market during the last 15 years. Today more than 46% of consumer dollars spent in the United States on toilet soaps go for deodorant and antibacterial bars. The success of these products is based on their performance under actual conditions of use. Antibacterial soaps play an important role in hospital and clinical usage, as well as in hygiene and in providing effective deodorant action. Moreover, by substantially reducing the cutaneous bacterial population, they can be valuable aids in protecting against minor skin disorders and secondary infections.

Today's toilet soaps for which antibacterial claims are made must meet the same federal standards for safety and efficacy as any other drugs. Antibacterial soaps however are mass-market, consumer products and, although they fulfill an important role, they are not miracle drugs; care must be taken not to promote them as such.

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