Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1965, 33, 219-226

Candicidin and Other Polyenic Antifungal Antibiotics

A Review *

SELMAN A. WAKSMAN [1], HUBERT A. LECHEVALIER [2] & CARL P. SCHAFFNER [3]

About 50 polyenic antifungal antibiotics produced by actinomycetes have been isolated and described. Among these are the most effective antimonilial agents so far known. These polyenes can be classified into four broad groups depending on the number of conjugated carbon-to-carbon double bonds that are present in their chromophores. Only some of the tetraenes (four conjugated double bonds), such as nystatin and pimaricin, and a few heptaenes (seven conjugated double bonds), such as amphotericin B, Trichomycin candicidin and hamycin, have found practical application in the treatment of infectious diseases caused by fungi. Nystatin and pimaricin show the least in vitro *activity against fungi, while trichomycin and candicidin are the most active. Recent clinical investigations carried out in the USA have shown that candicidin is very effective in the treatment of vaginal monilial infections.*

In 1952, two of us in collaboration with two other members of the laboratory of the senior author prepared for the *Bulletin of the World Health Organization* a summary of what was then known about antifungal antibiotics (Waksman et al., 1952). At that time, we suggested that two groups of such substances could be recognized—namely, those that were active against fungi and bacteria and those that were active against fungi only. Of all the antibiotic-producing microbes, the actinomycetes were shown to offer the greatest potentialities as sources of antifungal agents. Six of the antibiotics listed were studied in further detail: fungicidin (now known as nystatin), fradicin, cycloheximide (Actidione), antimycin A, and two numbered preparations, C381 and C135. Antibiotic C135 was later named candicidin (Lechevalier et al., 1953). None of these preparations inhibited bacteria or actinomycetes, but they exerted a marked effect upon the growth of fungi, especially yeast forms.

During the past fourteen years, an extensive literature has accumulated on the production of antifungal antibiotics by actinomycetes.[4] These substances can be divided into a number of groups of substances, the most important of which are the polyenes. This group includes four subgroups: the tetraenes, the pentaenes, the hexaenes, and the heptaenes. With the exception of nystatin, which is a tetraene, all the important antifungal polyenic agents from actinomycetes that have found practical application belong to the heptaenes. These are also the most frequently produced polyenes (Pledger & Lechevalier, 1956; Vaněk et al., 1958; Oroshnik & Mebane, 1963).

The isolation of large numbers of antifungal antibiotics was made possible through various screening programmes, using one or more fungi as test organisms. Schatz & Hazen reported in 1948 that, out of 243 cultures of actinomycetes isolated from various soils, 124 (51%) were antagonistic to one or more of the following fungi: *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton gypseum*, and *T. rubrum*. Ball et al. (1957) carried out an extensive screening programme for antifungal antibiotics, using soils collected from all parts of the world; the ratio of polyenic to non-polyenic antibiotics was 20 : 1.

POLYENES

With the exceptions of griseofulvin and variotin, which are produced by fungi, nearly all the important antifungal antibiotics are produced by actinomycetes

* From the Institute of Microbiology, Rutgers—The State University of New Jersey, New Brunswick, N.J., USA.

[1] Professor Emeritus, Microbiologist.

[2] Associate Professor, Microbiologist.

[3] Associate Professor, Chemist.

[4] The literature on this subject has been extensively reviewed by Waksman & Lechevalier (1962), Waksman (1963) and Řeháček (1964).

and are polyenic in nature. Among the important non-polyenic products, one should mention cycloheximide, an actinomycetic product mainly used against plant pathogens.

The polyenes possess similar chemical properties (Drouhet, 1958), but they can be largely distinguished by their characteristic light-absorption spectra. This is due to the presence in the molecule of a series of conjugated unsaturated double bonds (Oroshnik et al., 1955). They are unstable compounds, especially in the light and in acidic or alkaline solutions. They are not readily soluble in non-polar solvents or in water. Their high activity upon pathogenic yeasts and yeast-like fungi tended to render these antibiotics extremely valuable in the treatment of various fungal infections in man and in animals not otherwise subject to therapy. The recent extensive use of tetracyclines in human and animal therapy tends to favour moniliasis and other infections due to yeast-like fungi. This further necessitated the use of polyenes for the treatment of such secondary infections. The polyenes are usually produced by cultures of actinomycetes, some of which also form other antibiotics.

Nearly 50 polyene antibiotics have now been isolated, many of which have been crystallized. On the basis of their absorption of light, they are usually separated into four major subgroups, based upon the presence of a chain of four, five, six or seven conjugated double bonds. Their chemical and biological properties have been summarized in various reports (Neelameghan, 1960; Vining, 1960; Drouhet, 1963).

Tetraenes

Fungicidin, later designated as nystatin, is a tetraene. It was the first polyenic antibiotic isolated (Hazen & Brown, 1950) from a culture of *Streptomyces noursei*. It found extensive practical application in the treatment of monilial and other infections caused by yeast-like fungi (Dutcher, 1957; Lampen, 1962). Other tetraene antibiotics later isolated include rimocidin, chromin, antimycoin, sistomycosin, pimaricin, etruscomycin, unamycin, protocidine, and akitamycin. None of these has found, so far as is known, any practical application.

Pentaenes

Eurocidin was probably the first pentaene isolated (Nakazawa, 1955) from actinomycete cultures. Among the other pentaenes now known, mention may be made of fungichromin, fungichromatin, pentamycin, filipin, lagosin, moldcidin, and aliomycin. None of these has so far found any practical application.

Hexaenes

Flavacid was the first hexaene obtained from a culture of *Streptomyces flavus* (Takahashi, 1953). Among the other known hexaenes, one may mention mediocidin, endomycin, and cryptocidin. None of them has been highly purified and none has found practical application.

Heptaenes

This group of polyenic antibiotics contains some of the most important antifungal agents that have found application in human and animal therapy. Candicidin, Trichomycin and ascosin were the earliest reported. Later amphotericin B and candidin, and, more recently, hamycin were isolated and found to be highly effective. A number of other heptaenes have been isolated, such as perimycin, heptamycin and various others, designated by letter or by number.

The candicidin-producing culture (a strain of *Streptomyces griseus*) was first isolated in 1948 from a sample of cow manure (Lechevalier et al., 1953). An antibiotic preparation obtained from this culture (C135) was highly active upon yeasts and yeast-like fungi, but not upon filamentous fungi, and had no activity upon bacteria. It was named candicidin because of its high activity on *Candida albicans*.

Candicidin was found to be similar, in its light-absorption spectrum, to ascosin, but was quite distinct from nystatin, antimycoin, chromin, and rimocidin. Further studies (Vining et al., 1954) brought out the fact that candicidin was closely related to ascosin (Hickey et al., 1952), and trichomycin (Hosoya et al., 1952). Another antibiotic, candidin (Vining et al., 1955), also isolated in our laboratory, differed from the ascosin-candicidin-Trichomycin type. A comparison of four polyenes pointed to a very high activity of candicidin (see the table).

These four polyenes, when tested on a solid medium, were more active against growing fungi at a neutral pH than at an acid pH. In a liquid medium, differences in activity at various pH values were less striking. The activity of candicidin varied with pH more than that of the other three polyenes. Nystatin was least affected by pH variations.

EFFECT OF FOUR POLYENIC ANTIFUNGAL ANTIBIOTICS AT TWO DIFFERENT pH VALUES [a]

Antibiotic	Minimum inhibitory concentration [b] (μg/ml)						
	C. albicans			*S. cerevisiae*		*A. niger*	
	pH 4.5	pH 7.0	Ratio pH 4.5/ pH 7.0	pH 4.5	pH 7.0	pH 4.5	pH 7.0
Nystatin	4.5	1.6	2.8			5.7	1.7
Candidin	0.5	0.12	4.2	0.40	0.11		
Amphotericin B	0.5	0.15	3.3	0.43	0.09		
Candicidin	0.057	0.005	11.5	0.025	0.001	0.7	0.1

[a] Reproduced, by permission, from Lechevalier (1960).
[b] Average of three assays.

IN VIVO ACTIVITIES OF POLYENE ANTIBIOTICS

The polyenes conform to a general pattern of toxicity and antimicrobial activity, exhibiting varying degrees of action against many species of fungi (Gerke & Madigan, 1961). They have no effect upon the growth of bacteria, but in some cases they are active against certain protozoa (Furtado, 1960). Polyene antibiotics can be tolerated orally in relatively large doses but parenterally they show a considerable degree of toxicity even in limited amounts (Drouhet, 1958). Water-soluble *N*-acetyl derivatives—candidin, amphotericin B, candicidin and Trichomycin—were found to be less toxic (Lechevalier et al., 1961) and less active than the parent compounds.

Nystatin has found extensive application in the treatment of various fungal diseases in man and in animals (Drouhet, 1955). It was particularly effective in the treatment of moniliasis caused by *Candida albicans*. Another antifungal antibiotic of the nystatin type was isolated from a culture of *S. aureus* by Raubitschek et al. (1952). It exerted a protective action against *C. albicans* in embryonated eggs.

Trichomycin, a heptaene, was isolated in 1950 from a culture of *S. hachijoensis* by Hosoya et al. (1952). Later, it was found to be very effective in the treatment of vulvo-vaginitis caused by species of *Candida* (Magara et al., 1955). Vaginal suppositories containing 50 mg of Trichomycin were used once daily for a period of four days. When administered locally and orally, it resulted in almost complete recovery of the patient from vaginitis and vaginal candidiasis. No toxicity was noted. Trichomycin was also an effective agent against *Trichophyton* infections and other types of dermatomycosis (Magara et al., 1955; Hosoya et al., 1954).

Fungimycin (syn. perimycin) was isolated in 1952 in crude form by Wooldridge and Hoffmann from a culture later designated as *S. coelicolor* var. *aminophilus*. Further chemical investigations (Borowski et al., 1960) showed it to be a unique member of the aromatic subgroup of heptaene antibiotics.

Amphotericin was isolated (Gold et al., 1956) from a culture of *S. nodosus* found in a Venezuela soil. It was a mixture of two compounds (A and B). These possessed low toxicity and were active in infections caused by *Candida albicans*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, and *Trichophyton mentagrophytes* (Steinberg et al., 1956). Amphotericin B, a heptaene, proved to be more effective than amphotericin A, a tetraene. When used intravenously, it was effective (Seabury, 1961) in the treatment of blastomycosis, cryptococcosis, histoplasmosis, and sporotrichosis. Other deep-seated mycoses were also found to be sensitive to it (de Baislcumbert, 1963). Its effect upon leishmaniasis was also established (Cappuccino & Stauber, 1959; Furtado, 1960).

Candidin was isolated (Taber et al., 1954) from a culture of *S. viridoflavus*, and found to be similar in its properties and activities to amphotericin B. It was more active *in vivo* (Solotorovsky et al., 1958) against *H. capsulatum* and *C. albicans* than nystatin and certain other antifungal agents.

Hamycin was isolated by Thirumalachar et al. (1961) in India from a culture of *S. pimprina*. It was effective in cases of otomycosis, seborrhaeic dermatitis, trichomonal vaginitis, and *Cryptococcus neoformans* infections (Atre et al., 1961; Gokhale et al., 1963; Padhye & Thirumalachar, 1963).

Various fungi can be made resistant to the polyene antibiotics *in vitro*, but *in vivo* resistance has

been difficult to obtain. The extensive clinical use of various polyenes brought out the fact that these antibiotics do not induce readily sensitization.

CANDICIDIN

Chemistry

Candicidin is a heptaenic macrolide antifungal antibiotic, produced by a strain of *Streptomyces griseus* isolated in 1948 and at first designated by a number (C135), and only later named candicidin. The isolation and preliminary characterization were first reported by Lechevalier et al. in 1953, and later by Vining et al. in 1955. Crude preparations exhibited remarkable spectral absorption in the ultraviolet visible regions, indicative of highly conjugated unsaturated systems. It was found to be insoluble in water and unstable in aqueous suspensions.

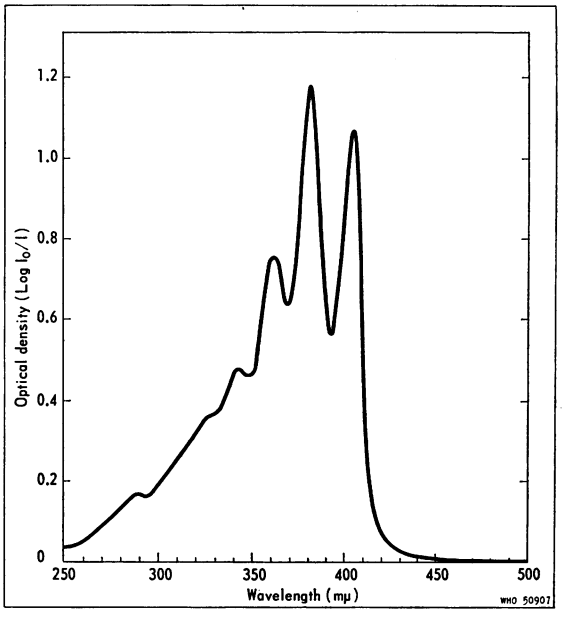
Since 1950 several other antibiotic substances with similar or related spectral characteristics have also been described. Oroshnik et al. (1955) pointed out that all these antibiotics could be definitely characterized as conjugated polyenes rather than as polyenynes. Thus candicidin at the time was classified as a heptaene. The lack of pure preparations and the possible presence of stereoisomers made the fine interpretation of the heptaene spectra most complicated. In contrast to shorter polyenic chromophores, many of the heptaene antibiotics do not exhibit all-*trans* chromophores.

The first preparations of candicidin and other heptaenes were usually quite impure. The unstable and very complex nature of these substances made purification and differentiation most difficult problems. As a result, numerous methods were investigated (Schaffner & Borowski—in preparation) before adequate procedures for the purification of candicidin could be found.

From cultural broths of *Streptomyces griseus* candicidin is isolated by precipitation at acid pH and filtration on Hyflo supercel. Resolubilization at higher pH and solvent extraction followed by concentration under reduced pressure produce very crude, highly-coloured preparations of candicidin of approximately 20% purity. Considerable purification of this crude preparation is achieved by solution and precipitation from pyridine/acetic-acid/water solvent systems followed by thorough acetone washings. A yellow candicidin preparation of approximately 70% purity is obtained. Subjected to further purification by countercurrent distribution in the solvent system, pyridine/ethyl-acetate/water (3.5-6.5-8.3 v/v) with the application of 100 transfers, a golden-yellow amorphous candicidin preparation of approximately 90% purity is obtained. Final purification is achieved by repeating the precipitation from pyridine/acetic-acid/water mixtures. Purification of candicidin cannot be readily obtained directly by crystallization. Only pure candicidin can be crystallized. Candicidin crystallizes as small, spherically arranged needles or rosettes from aqueous tetrahydrofuran or pyridine/acetic-acid/water solution.

Pure candicidin exhibits $E^{1\%}_{1cm} = 1150$ at 380 mμ. The absorption spectrum of crystalline candicidin is given in the accompanying figure. It can be seen that with crystalline candicidin major absorption maxima are to be found at 403 mμ, 380 mμ and 360 mμ. The fact that the longest wavelength absorption peak at 430 mμ is shorter than that at 380 mμ seems to indicate the presence of some internal *cis* double-bonding or internal branching. The position of the absorption peaks is located a few millimicrons towards the shorter wavelength as compared with that expected for α, ω-disubstituted or straight chain all-*trans* heptaene chromophores.

LIGHT ABSORPTION SPECTRUM OF CRYSTALLINE CANDICIDIN [a]



[a] μg/ml in methanol.

This also supports the suggestion of the presence of internal *cis* double-bondings in the chromophore.

Candicidin, unlike some other heptaene antibiotics, consists of a single component. Extensive countercurrent distribution studies in several solvent systems support this observation. Pure candicidin is insoluble in water, alcohols, ketones, esters, ethers, hydrocarbons and other lipophylic solvents. It is soluble in dimethylsulfoxide, dimethylformamide, pyridine and lower aliphatic acids. The addition of 5%-25% water to alcohols greatly increases the solubility. Candicidin does not form soluble salts in acids. However, soluble salts are formed in alkaline solution (pH 10-11). Candicidin exhibits particularly excellent solubility in 80% aqueous tetrahydrofuran solution.

Candicidin is a macrocyclic lactone or macrolide. All heptaene macrolides examined to date contain only C, H, O, and N. Crystalline candicidin on elementary analyses revealed C, 63.29%; H, 7.16%; O, 25.63%; N, 2.33%; C-CH_3, 5.13%—corresponding to a tentative empirical formula of $C_{63}H_{85}O_{19}N_2$, considering the molecular weight from a neutralization equivalent as an acid of 1200 and the presence of two nitrogens in the molecule.

The nitrogens present in candicidin are basic. Acid hydrolysis or methanolysis liberates the amino sugar, mycosamine (3-amino-3,6-dideoxy-D-mannose). This unusual amino sugar has been commonly found in most of the other polyene antibiotics. The fact that candicidin on treatment with aqueous sodium hydroxide liberates the aromatic amine, *p*-aminoacetophenone, by an alkaline retrograde dealdolization mechanism accounts for the second basic nitrogen in the molecule. Thus candicidin has been classified (Schaffner & Borowski, 1961) as belonging to the aromatic structural subgroup of heptaenes.

Candicidin also contains a free carboxyl group present as a zwitterion indicated by a strong peak in the infra-red spectrum at 6.40 μ. At the same time a sharp peak at 5.87 μ indicates the presence of an unstrained lactone. Saponification of candicidin results in complete biological inactivation. When candicidin as the *N*-acetylated derivative is reduced with sodium borohydride, the product does not liberate *p*-aminoacetophenone on treatment with alkali, suggesting the presence in candicidin of a carbonyl function adolically linked to the aromatic amine. Considering the empirical formula tentatively proposed for candicidin ($C_{63}H_{85}O_{19}N_2$), the presence of mycosamine, lactone, carboxyl and carbonyl groupings only partially accounts for the large amount of oxygen in the molecule. A good part, if not all, of the remaining oxygen atoms in candicidin exist as hydroxyl groups.

In review, candicidin is a large-ring lactone or macrolide possessing a heptaenic chromophore and aromatic amine side-chain imparting a lipophylic character. As hydrophylic substituents the macrolide possesses numerous hydroxyl groups, a glycosidically attached amino sugar, and a free carboxyl group. The alkaline instability of candicidin may be attributed to the lactone and the acid instability to the amino sugar and polyenic chromophore. The latter is also subject to oxidative degradation.

In vitro *activity*

Candicidin inhibits the growth of a large number of fungi. It inhibits *Candida* species with 0.5 μg/ml to 50 μg/ml (Kligman & Lewis, 1953; Drouhet, 1958; McCoy & Kiser, 1959; Lechevalier, 1960). An increase in minimal inhibitory concentration of a strain of *C. albicans* from 0.25 μg/ml to 1.5 μg/ml was induced by 15 passages of the organism in candicidin-containing media (Lechevalier et al., 1953).

In vivo *activity*

The first *in vivo* evaluation of candicidin was made by Kligman & Lewis in 1953. It was found to protect mice infected with *Candida albicans*, *Blastomyces dermatitidis*, and *Sporotrichum schenckii*, but had only a partial protective effect on torulosis and histoplasmosis in mice. The oral LD_{50} of candicidin administered to mice was 90 mg/kg to 400 mg/kg, and the intraperitoneal LD_{50} was 2.1 mg/kg to 7.0 mg/kg. A 1% concentration of candicidin injected intradermally and subcutaneously in mice and guinea-pigs caused local tissue necrosis within 24 hours of injection but 0.3 ml of a 1% concentration caused no local irritation when placed in the conjunctival sac. A 1% concentration of candicidin did not irritate the human oral mucosa when applied to the mouth for three minutes every three hours for two days.

The administration of 0.75 mg of candicidin intraperitoneally daily for ten days starting on the day of infection had a protective effect upon mice infected with *C. albicans* and *Blastomyces dermatitidis*. It was of limited value, however, in controlling infection in animals caused by *Histoplasma capsulatum* and of no value whatsoever upon infection by *Cryptococcus neoformans*.

On comparing the activity of candicidin and nystatin against a standardized systemic *C. albicans* infection in mice, McCoy & Kiser (1959) found that candicidin protected 100% of the mice, whereas nystatin with twice the dosage protected only 60%.

Oswald & Pocurull (1960) reported for candicidin both a high fungistatic and fungicidal activity, especially against *Botrytis cinerea*, *Candida albicans*, *Cryptococcus neoformans*, *Microsporum audouini*, *Sporotrichum schenckii*, and *Trichophyton rubrum*. Stauber (1962) demonstrated the chemotherapeutic property of candicidin (and candidin) against visceral leishmaniasis.

Clinical studies

Franks et al. (1954) treated with candicidin three patients with freshly contracted monilial intertrigo; the infection cleared up after 10 days of treatment with the water-insoluble form of the drug (using polyethylene glycol as carrier). A chronic case responded after seven weeks, but later relapsed. Three cases of paromonilia failed to respond; these four cases were all treated with the water-soluble form of the drug. Fox (1955) reported a case of mycotic vulvovaginitis treated with candicidin; the results were excellent; it was suggested that " candicidin is certainly worthy of further consideration ".

Because of the major interest that was being centred in the early years of the " antibiotic era " upon the antibacterial antibiotics, relatively little attention was being paid to the antifungal agents, in spite of the recognition that the use of certain, so-called " broad spectrum," antibiotics tended to favour the development of moniliasis. The fact that a few compounds were already available appeared to obviate the need for others. Nystatin, amphotericin B and Trichomycin were among those introduced into early use. A known antibiotic, derived from a fungus, but remaining dormant for several years—namely, griseofulvin—also became available only recently for the treatment of dermatophitic infections.

It took several years, therefore, before the interest in candicidin was aroused again, based largely upon its known high potency against yeast-like fungi. A series of publications has appeared recently. Abruzzi (1964) treated 100 patients (43 gravid and 57 non-gravid) suffering from vaginal infections caused by *Candida albicans*, as established by clinical symptoms and by isolation cultures. The patients were treated twice daily, with 1-g vaginal tablets containing 3 mg of candicidin. A cure rate of 90% was obtained. The treatment was particularly effective, and even ideal, for pregnant patients.

Giorlando et al. (1964) treated 154 patients, of whom 74 were pregnant. With different amounts of candicidin and different periods of treatment, a recovery of 90%-100% was obtained. Melges (1964) reported similar results, both symptomatically and therapeutically, for a group of 48 patients; no untoward reactions were noted.

Olsen (1965) treated 51 patients suffering from moniliasis with candicidin. One course of treatment resulted in an 88% cure rate and a second course increased this rate to 96%. Friedel (1965) treated 51 white obstetrical and gynaecological patients established as having monilial vaginitis through cultural studies. Those treated with candicidin tablets gave 78% initial cures and 93% after re-treatment of stubborn cases. The ointment gave 100% favourable effects.

Roberts & Sullivan (1965) treated 25 patients suffering from monilial vaginitis; 10 of these patients were pregnant. The 15 non-gravid patients and eight of the 10 gravid patients were cured by the use of candicidin ointment; one of the two patients with a resistant condition was diabetic and the other had endocervicitis. Of 50 patients treated with candicidin tablets, 42 became free of vaginal moniliasis after one or two 14-day courses of home treatment and remained free of infection for one month following treatment, as proven by cultural studies.

These results bring out emphatically the growing recognition of the importance of candicidin in the treatment of various fungal infections, especially in obstetrical and gynaecological cases.

RÉSUMÉ

Près de 50 antibiotiques polyéniques produits par des actinomycètes ont des propriétés antifongiques connues. Le premier isolé, la fungicidine (nystatine), fut largement employé dans le traitement des infections à levures, particulièrement des moniliases. Ces infections, jusque-là sans traitement actif, ont été favorisées par l'usage extensif des tétracyclines chez l'homme et l'animal. Les antibiotiques polyéniques ont un mode d'action et de toxicité commun. Bien tolérés à doses relativement fortes par voie orale, ils sont très toxiques par voie parentérale,

même à faibles doses. Sans action contre les bactéries et les champignons filamenteux, les polyènes inhibent les levures et, dans certains cas, quelques protozoaires.

Produite par une souche de *Streptomyces griseus*, la candicidine doit son nom à son action particulièrement marquée contre *Candida albicans*. C'est un heptaène, comme l'amphotéricine B, la Trichomycine et l'hamycine. Elle ne cristallise que lorsqu'elle est pure. Son spectre d'absorption indique la présence de plusieurs doubles liaisons en position cis et de radicaux substitués sur le noyau. De formule présumée C_{63} H_{85} O_{19} N_2, elle contient deux groupements amines liés à un noyau lactone cyclique. Insoluble dans l'eau et de nombreux solvants organiques, elle est soluble dans le diméthylsulfoxyde, la diméthylformamide, la pyridine, les acides aliphatiques inférieurs et le tétrahydrofurane en solution aqueuse à 80%.

In vitro, la candicidine est particulièrement active contre *C. albicans*. *In vivo*, chez la souris, sa DL_{50} est de 90-400 mg/kg par voie orale et de 2,1-7 mg/kg par voie intrapéritonéale. Elle protège les souris contre les infections à *C. albicans*, *Blastomyces dermatitidis*, *Botrytis cinerea*, *Microsporum audouini*, *Sporotrichum schenckii*, *Trichophyton rubrum* et, pour certains auteurs, *Cryptococcus neoformans*. Elle a une action limitée sur l'infection à *Histoplasma capsulatum*, et est active dans les leishmanioses viscérales. A doses égales, la candicidine est plus efficace que la nystatine contre les candidoses expérimentales.

Cliniquement, la candicidine a montré une activité marquée dans le traitement des moniliases vaginales. Cent malades présentant une infection vaginale à *C. albicans* furent guéries dans 90 % des cas après dix jours de traitement par application deux fois par jour de comprimés vaginaux contenant 3 mg de candicidine. Certains expérimentateurs, chez d'autres groupes de malades, observèrent des taux de guérison de 88, 96, 78 et 93%. L'application de la candicidine en pommade a parfois donné de meilleurs résultats. Certaines de ces guérisons ont été vérifiées par la recherche des *Candida* en culture. La tolérance a toujours été bonne, particulièrement chez des femmes enceintes. Deux cas résistant au traitement présentaient l'un un diabète, l'autre une endocervicite.

REFERENCES

Abruzzi, W. A. (1964) *West. Med.*, **5**, 62

Atre, W. G., Wakankar, P. S. & Padhye, A. A. (1961) *Hindustan Antibiot. Bull.*, **3**, 172-173

Baislcumbert, P. de (1963) *Chemotherapia (Basel)*, **6**, 51-57

Ball, S., Bessell, G. J. & Mortimer, A. (1957) *J. gen. Microbiol.*, **17**, 96-103

Borowski, E., Schaffner, C. P., Lechevalier, H. & Schwartz, B. S. (1960 *Antimicrob. Ag. Ann.*, p. 532-538

Cappuccino, E. F. & Stauber, L. A. (1959) *Proc. Soc. exp. Biol. (N.Y.)*, **101**, 742-744

Drouhet, E. (1955). In: Sternberg, T. H. & Newcome, V. D., ed., *Therapy of fungus diseases*, Boston, Little, Brown & Co., p. 211-218

Drouhet, E. (1958) *The therapeutic use of antifungal antibiotics*. In: Riddle, R. W. & Stewart, G. T., ed., *Fungous diseases and their treatment*, London, Butterworth, p. 192

Drouhet, E. (1963) *Antibiot. et Chemother. (Basel)*, **2**, 21-50

Dutcher, J. D. (1957) *Monog. on Ther.*, **2**, 87

Fox, J. L. (1955) *Antibiotic Med.*, **1**, 349-350

Franks, A. G., Taschdjicin, C. L. & Thorpe, G. A. (1954) *J. invest. Derm.*, **23**, 75-76

Friedel, H. J. (1965) *Maryland med. J.* (in press)

Furtado, T. A. (1960) *Antibiot. Ann., 1958-1960*, pp. 631-637

Gerke, J. R. & Madigan, M. E. (1961) *Antibiot. and Chemother.*, **11**, 227-237

Giorlando, S. W., Torres, J. F., & Muscillo, G. (1964) *Amer. J. Obstet. Gynec.*, **90**, 370-373

Gokhale, B. B., Bhagwat, P. D. & Joglekar, M. V. (1963) *Hindustan Antibiot. Bull.*, **5**, 96-97

Gold, W., Stout, H. A., Pagano, J. F. & Donovick, R. (1956) *Antibiot. Ann., 1955-1956*, pp. 579-586

Hazen, E. L. & Brown, R. (1950) *Science*, **112**, 423

Hickey, R. J., Corum, C. J., Hidy, P. H., Cohen, I. R., Nager, U. F. B. & Kropp, E. (1952) *Antibiot. and Chemother.*, **2**, 472-483

Hosoya, S., Komatsu, N., Soeda, M., Yuwagucki, T. & Sonoda, Y. (1952) *J. Antibiot. (Tokyo)*, **5**, 564-566

Hosoya, S., Soeda, M., Imamura, S., Okada, K., Nakazawa, S., Komatsu, N., Kobori, T., & Ikenaga, M. (1954) *G. ital. Chemioter.*, **1**, 217-230

Kligman, A. M. & Lewis, F. S. (1953) *Proc. Soc. exp. Biol. (N.Y.)*, **82**, 399-404

Lampen, J. O. (1962) *Fungi and fungous diseases*, New Brunswick, N.J., Squibb Institute for Medical Research, chapter 8

Lechevalier, H. (1953) *Presse méd.*, **61**, 1327-1328

Lechevalier, H. (1960) *Antibiot. Ann., 1959-1960*, pp. 614-618

Lechevalier, H., Acker, R. F., Corke, C. T., Haenseler, C. M. & Waksman, S. A. (1953) *Mycologia*, **45**, 155-171

Lechevalier, H., Borowski, E., Lampen, J. O., & Schaffner, C. P. (1961) *Antibiot. and Chemother.*, **11**, 640-647

McCoy, E. & Kiser, J. S. (1959) *Antibiot. Ann., 1958-1959*, pp. 903-909

Magara, M., Nittono, H., & Senda, T. (1955) *Antibiot. Med.*, **1**, 394-397

Melges, F. J. (1964) *Obstet. and Gynec.*, **24**, 921-923

Nakazawa, K. (1955) *Bull. agric. chem. Soc. Japan*, **29**, 650-652

Neelameghan, A. (1960) *Hindustan Antibiot. Bull.*, **2**, 131-155

Olsen, J. R. (1965) *Lancet* (in press)

Oroshnik, W. & Mebane, A. D. (1963) *Fortschr. Chem. org. NatStoffe*, pp. 18-79

Oroshnik, W., Vining, L. C., Mebane, A. D. & Taber, W. A. (1955) *Science*, **121**, 147-149

Oswald, E. J. & Pocurull, D. (1960) *Antibiot. and Chemother.*, **10**, 285-286

Padhye, A. A. & Thirumalachar, M. J. (1963) *Hindustan Antibiot. Bull.*, **6**, 41-43

Pledger, R. A. & Lechevalier, H. (1956) *Antibiot. Ann., 1955-1956*, pp. 249-254

Raubitschek, F., Acker, R. F., & Waksman, S.A. (1952) *Antibiot. and Chemother.*, **2**, 179-183

Řeháček, Z. (1964) *Classification of nonpolyenic antifungal antibiotics produced by actinomycetes.* In: Sylvester, J. C., ed., *Antimicrobial agents and chemotherapy 1963*, Ann Arbor, Mich., American Society for Microbiology, pp. 530-540

Roberts, C. L. & Sullivan, J. J. (1965) *Calif. Med.* (in press)

Schaffner, C. P. & Borowski, E. (1961) *Antibiot. and Chemother.*, **11**, 724-732

Schatz, A. & Hazen, E. L. (1948) *Mycologia*, **40**, 461-477

Seabury, J. H. (1961) *Chemotherapia (Basel)*, **3**, 81-94

Solotorovsky, M., Quabec, G. & Winsten, S. (1958) *Antibiot. and Chemother.*, **8**, 364-371

Stauber, L. A. (1962) *Sci. Rep. Ist. sup. Sanità*, **2**, 68-75

Steinberg, B. A., Jambor, W. D. & Suydam, L. O. (1956) *Antibiot. Ann., 1955-1956*, pp. 574-578

Taber, W. A., Vining, L. C. & Waksman, S. A. (1954) *Antibiot. and Chemother.*, **4**, 455-461

Takahashi, I. (1953) *J. Antibiot. (Tokyo)*, **6A**, 117-121

Thirumalachar, M. J., Menon, S. K. & Bhatt, V. V. (1961) *Hindustan Antibiot. Bull.*, **3**, 136-138

Vaněk, Z., Dolezilova, L. & Řeháček, Z. (1958) *J. gen. Microbiol*, **18**, 649-657

Vining, L. C. (1960) *Hindustan Antibiot. Bull.*, **3**, 37-54

Vining, L. C., Taber, W. A. & Gregory, F. J. (1955) *Antibiot. Ann., 1954-1955*, pp. 980-987

Vining, L. C., Taber, W. A. & Lechevalier, H. A. (1954) *Antifungal antibiotics of the candicidin type.* In: *Congrès international de Botanique. Rapports et communications parvenus avant le congrès aux sections 21 à 27*, Paris, pp. 106-110

Waksman, S. A. (1963) *Advanc. appl. Microbiol.*, **5**, 235-315

Waksman, S. A. & Lechevalier, H. A. (1962) *The actinomycetes. Vol. III. Antibiotics of actinomycetes*, Baltimore, Williams & Wilkins

Waksman, S. A., Romano, A. H., Lechevalier, H., & Raubitschek, F. (1952) *Bull. Wld Hlth Org.*, **6**, 163-172 [also in: *Microbial growth and its inhibition*, Geneva, pp. 163-172 (*World Health Organization : Monograph Series*, No. 10)]