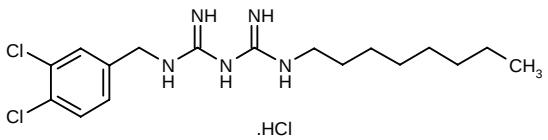
Drugs of the Future 1999, 24(2): 151-154

CCC: 0377-8282/99

OPB-2045

Antiseptic

1-(3,4-Dichlorobenzyl)-5-octylbiguanide hydrochloride



$C_{17}H_{27}Cl_2N_5.ClH$ Mol wt: 408.8022

CAS: 146509-94-6
CAS: 146510-36-3 (as free base)

EN: 248893

Synthesis

OPB-2045 can be obtained by several related ways: Scheme 1.

1) The addition of 3,4-dichlorobenzylamine hydrochloride (I) to sodium dicyanamide (II) in refluxing acetonitrile gives 1-(3,4-dichlorobenzyl)-3-cyanoguanidine (III), which is then condensed with octylamine hydrochloride (IV) in refluxing mesitylene (1-3).

2) The treatment of *S*,*S*'-dimethyl(cyanoimino)dithiocarbonate (V) with aqueous ammonia and further reaction with 3,4-dichlorobenzylamine hydrochloride (I) yields intermediate (III), which is then condensed with (IV) as before (1,2).

3) By condensation of 3,4-dichlorobenzylamine hydrochloride (I) with 1-cyano-3-octylguanidine (VI) in refluxing mesitylene (3).

Description

White edged crystals, m.p. 177-9 °C; lactate, m.p. 45-6 °C; glycolate, m.p. 109-10 °C; mesylate, m.p. 174-6 °C; hydrobromide, m.p. 120-1 °C; phosphate, m.p. 96-8 °C; dimesylate, m.p. 171-2 °C (2).

Introduction

The development of antiseptics dates back to the 1930s with the identification of antimicrobials that when applied topically, kill microorganisms or inhibit their reproduction or metabolic activities. Although studies have shown that the use of antiseptics by health care personnel is more effective in reducing microorganisms than control vehicles (4), controversy exists as to which agents are the most effective and safe (5-9).

The chronological development of antiseptics is presented in Table I. Although no new antiseptics have been launched in more than 20 years, the search for more potent, broad-spectrum antiseptics continues. Scientists at Otsuka designed and synthesized a series of 1,5-disubstituted biguanidines and the bactericidal activity of the resulting compounds was determined. Among these biguanidines, the 3,4-dichlorobenzyl derivatives were found to exhibit particularly high bactericidal activity, and one compound, OPB-2045, was chosen as a candidate antiseptic (1-3).

Antibacterial Activity

The bactericidal activity of OPB-2045 was examined using a microplate assay in which a bacterial strain (1 million cfu/ml) was exposed to the agent for 3 min after which an aliquot was removed and placed in antiseptic-inactivating serum. The sample was then cultured and surviving organisms were counted. Bactericidal concentrations of OPB-2045 against Gram-positive *Staphylococcus aureus* and clinical isolates of methicillin-resistant *S. aureus*, and Gram-negative *Escherichia coli*, *Pseudomonas aeruginosa* and clinical isolates of *Burkholderia cepacia* 10 were ≤ 10 μg/ml for all strains. Further evaluation showed that the bactericidal concentration following a 30-s exposure of isolates of *S. aureus*, methicillin-resistant *S. aureus*, *S. epidermidis*, *Enterococ-cus faecalis*, *E. coli*, *Serratia marcescens* and *P. aeruginosa* to OPB-2045 were 20, 10, 5, 10, 20, 20 and 10 μg/ml, respectively (1). A similar study reported efficacy of OPB-2045 against *P. aeruginosa* with MIC and MBC values of 12.5 μg/ml (10).

Pharmacokinetics and Metabolism

The pharmacokinetics of OPB-2045 were presented in a study in which rats were administered the agent as a single oral dose (10, 100 and 1000 mg/kg) or by s.c.

L.A. Sorbera, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of OPB-2045

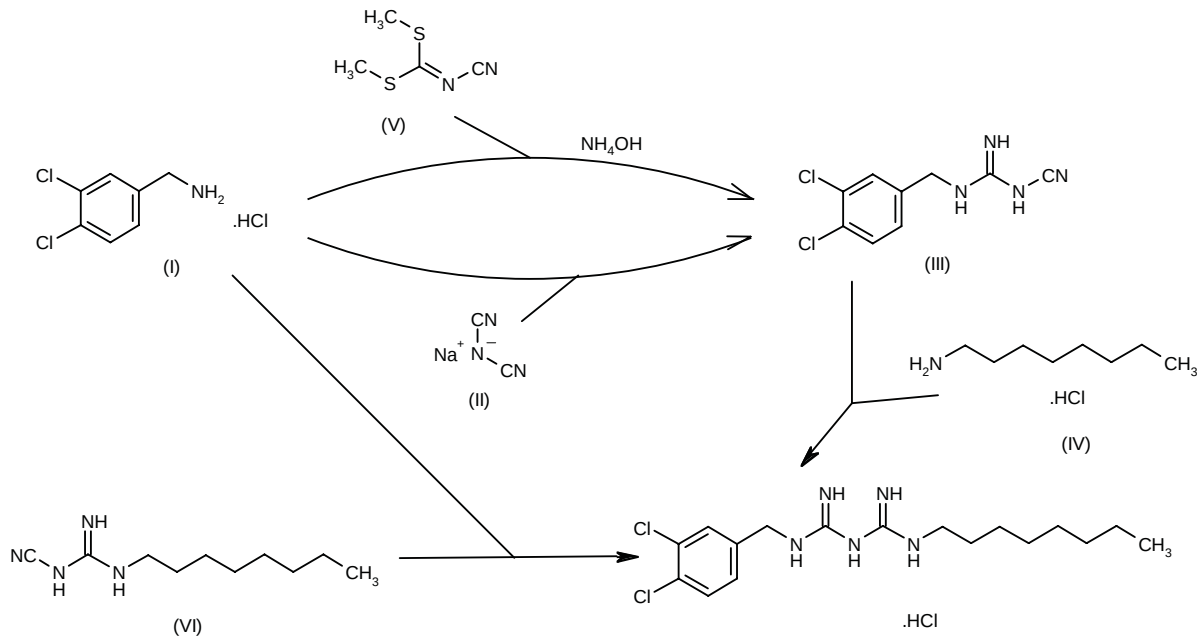


Table I: Chronological development of antiseptics.

Product	Type of compound	Year of introduction
Benzethonium chloride	Cationic surfactant	1943
Cetrinide	Cationic surfactant	1943
Hexachlorophene	Phenolic compound	1948
Dodicine	Amphoteric surfactant	1949
Benzalkonium chloride	Cationic surfactant	1951
Chlorhexidine gluconate	Chlorophenyl biguanide	1954
Povidone-iodine	Ionophore	1958
Triclocarban	Substituted carbanilide	1962
Silver sulfadiazine	Silver compound	1972
Taurolidine	Thiadiazine compound	1979

(1, 3, 10 and 30 mg/kg) or i.v. (1, 3 and 6 mg/kg) routes. A serum OPB-2045 concentration of < 15 ng/ml was detected only after administration of the oral dose of 1000 mg/kg. No dose-dependent increases in serum OPB-2045 were observed following s.c. administration and time courses were flat. Bioavailability of oral OPB-2045 appeared to less be than s.c. administration. However, adequate serum OPB-2045 profiles were obtained following i.v. administration using a two-compartment model (Akaike information criterion estimation of –3.0 to ~ 58.1). A biphasic decline was observed with half-lives of 0.25-0.32 h and 2.16-4.07 h in the α- and β-phase, respectively. Considerable diffusion of the agent was indicated since the volume of distribution in the β-phase was 9.8-19.8 l/kg. The total serum clearance obtained was 2.0-3.9 l/kg (11).

Absorption and excretion were examined in rats following a single oral dose of [^{14}C]-OPB-2045 (10 mg/kg). Serum levels of radioactivity reached 0.09-0.11 μg eq/ml 30 min after administration and radioactivity in blood cells accounted for 7.5-53.1% of the total radioactivity in blood. A half-life of 5.9-8.6 h was estimated at 2 and 24 h after administration and the AUC was 0.46-0.59 μg eq.h/ml. Urinary and fecal excretion at 168 h and biliary excretion at 24 h postdosing were 1.2-4.6%, 9.1-94.5% and 2.9%, respectively. No gender-related differences were observed (12).

Absorption, distribution and excretion were also examined in rats after a single s.c. dose of [^{14}C]-OPB-2045 (1 mg/kg). A C_{max} of 0.032-0.033 μg eq/ml was obtained in both male and female rats 1 h after administration. The half-life was 77.0 h at 48 and 168 h postdosing and AUC values were 0.75-0.78 μg eq.h/ml. Radioactivity in the blood cells accounted for 31.9-77.9% of the total radioactivity in the blood and was greater than that detected in serum; blood AUC was 1.5-2 times higher than the respective serum value. The highest amount of radioactivity 1 h postdosing was detected in the pituitary gland, followed by the thyroid gland, adrenal glands, lungs and kidneys in male and female rats, with 10-26 times greater concentrations found in tissues as compared to blood. Urinary and fecal excretion of radioactivity 168 h postdosing were 17.2-20.8% and 68.4-71.2% of the dose, respectively, and biliary and urinary excretion at 24 h were 34.1% and 14.2% of the dose, respectively (13).

Absorption, distribution and excretion were also examined in dogs given a single s.c. dose of [^{14}C]-OPB-2045 (1 mg/kg). A C_{max} of 0.074 μg eq/ml and a serum C_{max} of 0.084 μg eq/ml were obtained at 30 min postdosing. Blood half-lives of 29.5 h and 58.6 h were obtained at 30 min to 12 h and 12-168 h, respectively, as compared to serum half-lives of 34.4 h and 67.6 h, respectively. The AUCs for blood and serum were 5.4 and 6.03 μg eq.h/ml, respectively. The radioactivity in blood cells 30 min and 168 h after administration accounted for 28.3-46.5% of the total blood radioactivity. However, the highest level of radioactivity was found in the kidneys, followed by thyroid gland, pituitary gland, lungs, heart, liver and adrenal glands. Urinary and fecal excretion at 168 h were 59.4% and 23.5% of the dose, respectively (14).

The percutaneous absorption and tissue distribution of OPB-2045 were also evaluated in rats with intact or damaged skin given single or repeated topical applications of 0.1% [^{14}C]-OPB-2045 (0.3 mg/rat/6.25 cm^2 area). Results were compared with rats receiving a single dose (0.12 mg/rat/6.25 cm^2 area) of both 0.04% [^{14}C]-OPB-2045 and [^{14}C]-chlorhexidine. Only low levels of radioactivity were detected in serum at 1 and 8 h following administration of 0.1% [^{14}C]-OPB-2045 (0.002 ± 0.001 and 0.001 ± 0.001, respectively). Radioactivity in other tissues was extremely low except at the application site. Urinary and fecal excretion of radioactivity within 336 h of dosing were 1.2% and 4.1% of the dose, respectively, in rats with intact skin and 2.4% and 5.0%, respectively, in rats with damaged skin. The percutaneous absorption of OPB-2045 was found to be poor and similar to that of chlorhexidine, with results showing an estimated percutaneous absorption of 1.4% of the total dose in 0.1% [^{14}C]-OPB-2045-treated rats with intact skin, as compared to 4.2% in animals with intact skin receiving 0.04% [^{14}C]-OPB-2045 and [^{14}C]-chlorhexidine. The study also concluded that the stratum corneum did not influence absorption of OPB-2045 or chlorhexidine through the skin (15).

The metabolism of OPB-2045 was described for rats and dogs following s.c. administration of [^{14}C]-OPB-2045 (1 mg/kg). In rats, the metabolites identified in the urine included 6-[5-(3,4-dichlorobenzyl)-1-biguanidino] hexanoic acid (DM-210), 4-[5-(3,4-dichlorobenzyl)-1-biguanidino] butanoic acid (DM-212), 5-[5-(3,4-dichlorobenzyl)-1-biguanidino] pentanoic acid (DM-213) and 3,4-dichlorobenzoic acid, which accounted for 4.6, 1.6, 1.5 and 1.4% of the dose, respectively, 72 h postdosing; no excretion of the unchanged compound was detected. DM-210, DM-212 and DM-213 were excreted in bile with a combined excretion rate of 15.6% for the OPB-2045 dose at 24 h postdosing. Radioactivity retained at the injection site 1, 8 and 24 h postdosing accounted for 5.5%, 34.6% and 13.0% of the administered dose, respectively, with the unchanged compound accounting for 80.8% of the radioactivity. None of the metabolites were detected at the injection site, indicating that OPB-2045 was not metabolized by the skin (16). Similar results were obtained in dogs, with metabolites DM-210, DM-212 and D-213 detected in urine. Although no unchanged compound was found in urine, OPB-2045 was detected in feces at 2% of the dose (17).

Toxicity

The toxic effects of OPB-2045 on reproduction and development were recently examined in rats. Maternal animals were administered the agent (0.02, 0.2 and 2 mg/kg) on days 7-17 of gestation. Indurations and s.c. hemorrhage were observed at the site of injection with a dose of 2 mg/kg; however, no effects of the drug were observed on fetal body weight, mortality or morphology. The nontoxic dose of OPB-2045 was determined to be 2 mg/kg in regard to effects on reproductive performance in males and females, embryo-fetal development and development of offspring (18-20).

Reproductive and developmental toxicity studies of OPB-2045 were also performed in rabbits after s.c. administration of doses of 0.02, 0.2 and 1 mg/kg on days 6-18 of gestation. The nontoxic dose in this study was estimated to be 1 mg/kg with respect to effects on female reproduction and embryo-fetal development (21).

Clinical Studies

OPB-2045 is currently in phase III trials (22).

Manufacturer

Otsuka Pharmaceutical Co., Ltd. (JP).

References

1. Tsubouchi, H., Ohguro, K., Yasumura, K., Ishikawa, H., Kikuchi, M. *Synthesis and structure-activity relationships of novel antiseptics.* Bioorg Med Chem Lett 1997, 7: 1721-4.

2. Tsubouchi, H., Ohguro, K., Yasumura, K., Ishikawa, H., Kikuchi, M. *Synthesis and structure-activity relationships of new disinfectants.* 16th Symp Med Chem (Nov 27-29, Toyama) 1996, Abst 2-P-3.

3. Ishihara, H., Yusumura, K., Tsubouchi, H., Higuchi, Y., Tamaoka, H. (Otsuka Pharm. Co., Ltd.). *Biguanide derivs., manufacturing method thereof, and disinfectants containing the derivs.* EP 507317.

4. Bartzokas, C.A. et al. *Evaluation of skin disinfecting activity and cumulative effect of chlorhexidine and triclosan handwash preparations on hands artificially contaminated with Serratia marcescens.* Infect Control 1982, 8: 163-7.

5. Sebben, J.E. *Surgical antiseptics.* J Am Acad Dermatol 1983, 9: 759-65.

6. Rutala, W.A., Cole, E.C. *Antiseptics and disinfectants: Safe and effective?* Infect Control 1984, 5: 215-8.

7. Larson, E.L., Laughon, B.E. *Comparison of four antiseptic products containing chlorhexidine gluconate.* Antimicrob Agents Chemother 1987, 31: 1572-4.

8. Larson, E. *Guideline for use of topical antimicrobial agents.* Am J Infect Control 1988, 16: 253-66.

9. Bjerke, N.B. *Handwashing agents.* Infect Control 1987, 8: 384-5.

10. Sakagami, Y. et al. *Study of bactericidal mechanism of OPB-2045, a novel disinfectant, against Pseudomonas aeruginosa through morphological observation.* Jpn J Chemother 1998, 46(Suppl. A): Abst 286.

11. Kudo, S., Umehara, K., Odomi, M., Miyamoto, G. *Pharmacokinetics of OPB-2045 in rats: Systemic exposure following oral, subcutaneous, and intravenous administration.* Xenobiotic Metab Dispos 1998, 13: 330-6.

12. Kudo, S., Iwasaki, M., Sugimoto, K., Kodama, R., Odomi, M. *Absorption and excretion of OPB-2045 following a single oral administration to rats.* Xenobiotic Metab Dispos 1998, 13: 325-9.

13. Kudo, S., Iwasaki, M., Sugimoto, K., Kodama, R., Odomi, M. *Absorption, distribution and excretion of OPB-2045 following a single subcutaneous administration to rats.* Xenobiotic Metab Dispos 1998, 13: 1-7.

14. Kudo, S., Iwasaki, M., Sugimoto, K., Kodama, R., Odomi, M. *Absorption, distribution and excretion of OPB-2045 following a single subcutaneous administration to beagle dogs.* Xenobiotic Metab Dispos 1998, 13: 8-12.

15. Kudo, S., Furukawa, M., Okumura, H., Umehara, K., Odomi, M., Miyamoto, G. *Percutaneous absorption and tissue distribution of 1-(3,4-dichlorobenzyl)-5-octylbiguanide (OPB-2045) in rats.* Xenobiotic Metab Dispos 1998, 13: 13-20.

16. Kudo, S., Umehara, K., Odomi, M., Miyamoto, G. *Metabolism of a new bactericidal antiseptic, OPB-2045, in rats following subcutaneous administration.* Xenobiotic Metab Dispos 1998, 13: 346-50.

17. Kudo, S., Umehara, K., Morita, S., Uchida, M., Miyamoto, G., Odomi, M. *Metabolism of 1-(3,4-dichlorobenzyl)-5-octylbiguanide in the dog.* Xenobiotica 1998, 28: 507-14.

18. Takenaka, T., Tamagawa, M. *Reproductive and developmental toxicity studies of OPB-2045 (2). Embryo-fetal development study in rats by subcutaneous administration.* Jpn Pharmacol Ther 1998, 26(2): 41-6.

19. Takenaka, T., Tamagawa, M. *Reproductive and developmental toxicity studies of OPB-2045 (1). Fertility study in rats by subcutaneous administration.* Jpn Pharmacol Ther 1998, 26(2): 35-40.

20. Takenaka, T., Tamagawa, M. *Reproductive and developmental toxicity studies of OPB-2045 (4). Pre- and postnatal development study in rats by subcutaneous administration.* Jpn Pharmacol Ther 1998, 26(2): 55-62.

21. Takenaka, T., Tamagawa, M. *Reproductive and developmental toxicity studies of OPB-2045 (3). Teratogenicity study in rabbits by subcutaneous administration.* Jpn Pharmacol Ther 1998, 26(2): 47-53.

22. Otsuka Pharmaceutical Co., Ltd. Company Communication Feb 1, 1999.