Properties of chlorhexidine dental varnishes EC40 and BioC

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EVIDENCE BASED PRACTICE

Caries prevention and control of mutans streptococci

Caries develops as a result of the production of lactic and acetic acids in the dental plaque. Mutans streptococci are the most important acid producers. High numbers of mutans streptococci on the teeth increase the risk of caries. The main species of mutans streptococci are *S. mutans* and *S. sobrinus*. Both species have a high capacity to produce acids, mainly lactic acid, from dietary sugars including saccharose, glucose, fructose and lactose. The cornerstones of caries prevention are the use of fluoride, control of the cariogenic microflora, the restriction of sugar consumption and good dental hygiene. Van Loveren (1994) has pointed out the importance of selective suppression of the mutans strepto cocci and the possibilities for this with the aid of chlorhexidine products. Patients with high numbers of mutans streptococci are better protected by regular chlorhexidine applications than by fluoride applications (Lindquist et al., 1989). Chlorhexidine gel applications have the disadvantage that they have to be repeated frequently if they are to be effective.

Compared with the application of chlorhexidine gel, the use of chlorhexidine varnish is efficient and comfortable for the patient. Daily rinsing with chlorhexidine mouth rinses have little effect against mutans streptococci. Moreover, these daily rinses with chlorhexidine result in brown-staining of oral mucosa, in particular of the tongue. In order to be effective, gel applications must be repeated several times on successive days. Concentrated chlorhexidine varnishes such as EC40 and BioC lack these disadvantages and therefore are the products of choice for use in the mouth.

- Lindquist B, Edwards S, Torell P, Krasse B. Effect of different caries preventive measures in children highly infected with mutans streptococci. Scand J Dent Res 97: 330-337, 1989.
- Van Loveren C. Cariëspreventie met chloorhexidine. (Caries prevention with chlorhexidine) Ned Tijdschr Tandheelk 101: 180- 182, 1994.
- Matthijs S, Adriaens PA. Chlorhexidine varnishes: a review. J Clin Periodontol 29: 1-8, 2002.
- Van Rijkom HM, Truin GJ, van 't Hof MA. A meta-analysis of clinical studies on the caries- inhibiting effect of chlorhexidine treatment. J Dent Res 75: 790-795, 1996.

Composition and properties of BioC and EC40

Both BioC and EC40 are supersaturated solutions of chlorhexidine diacetate in alcohol. The solution is stabilised by sandarac. Sandarac is a naturally occurring resin which in the past was used as a filling material in dentistry. Sandarac also has an antimicrobial potential. By virtue of their particular composition, BioC and EC40 have a very strong bactericidal activity. The percentage composition of the preparations is as follows:

BioC: chlorhexidine diacetate: sandarac: ethanol = 20: 37: 43

EC40: chlorhexidine diacetate: sandarac: ethanol = 35: 27: 38

The saturation concentrations of chlorhexidine diacetate in water and ethanol are approximately 2% and 12% (w/v), respectively. As a consequence of the high supersaturation, chlorhexidine diacetate crystallises out when BioC and EC40 come into contact with the tooth surface and saliva. As a result, micro-deposits of chlorhexidine diacetate will be formed on the surface and **in the pores** of the enamel and dentine. The long-term release of chlorhexidine from the micro-deposits is supported by

the fairly low solubility of chlorhexidine diacetate in water. The slow release from the varnish applied ensures that the concentration of chlorhexidine diacetate in the saliva remains low. As a result irritation of the oral mucosa, which occurs when concentrated gels or solutions of the water soluble chlorhexidine digluconate are used, is largely prevented.

A contact time of 5 to 10 minutes is adequate for BioC and EC40 to have a good effect. On removal of BioC and EC40 by the dentist or patient the micro-deposits of chlorhexidine diacetate remain behind in the pores of the enamel and dentine, as a result of which long-term action is ensured.

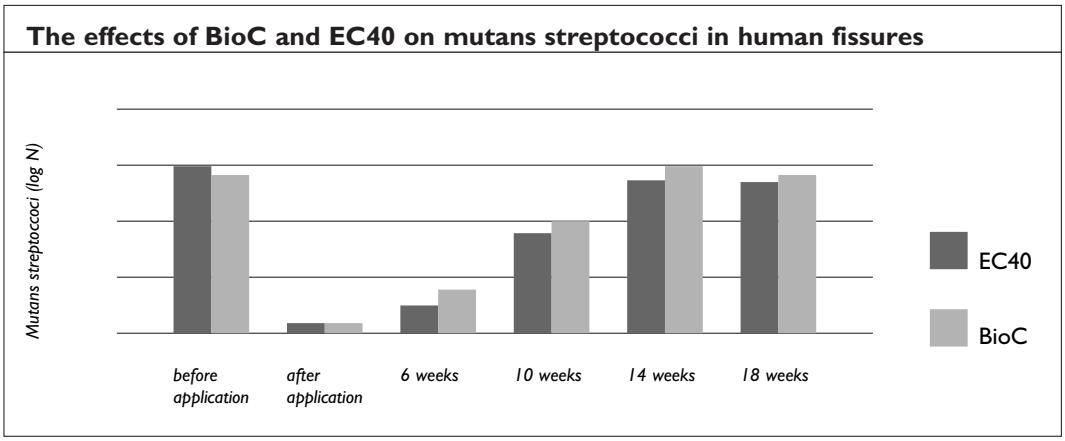
- Schaeken MJM, van der Hoeven JS, de Haan P, Lerk CF. Antimicrobial composition with long-term activity. European Patent specification, publication number 0 428 520 B1, 1993.

The main clinical effects of BioC and EC40

1. Suppression of mutans streptococci
Both preparations were developed for the effective suppression of mutans streptococci on the dentition. *Figure 1* shows the effects of BioC and EC40 on the numbers of mutans streptococci in human fissures.

Figure 1 »

The effects of BioC and EC40 on mutans streptococci in human fissures



After the treatment with chlorhexidine varnishes, mutans streptococci slowly return on the dentition. The figure shows that 10 weeks after treatment, the number of mutans streptococci is still at least 2 log units, that is 100-times, lower than before treatment. EC40 has the strongest effect on mutans streptococci, but the differences between BioC and EC40 are relatively small.

2. Inhibition of dental caries
See p.7 Caries reduction in man.

3. Inhibition of dental plaque
The inhibition of dental plaque formation by chlorhexidine varnishes was demonstrated in various clinical studies. Cosyn et al. (2005) used a 3-day plaque regrowth model and found that EC40 was effective in the inhibition of de novo plaque formation. Long-term inhibition of plaque formation was found following the treatment with EC40. Even 3 weeks after treatment plaque reduction was still significant (Tütücü et al., 1999).

4. Inhibition of dental calculus

Evidence for the inhibition of calculus formation by chlorhexidine varnish treatment comes from a clinical study by Fischer (2001). The observation is confirmed by oral reports from dental practitioners.

5. Inhibition of gingival inflammation

BioC and EC40 are strongly effective against the subgingival microflora and the varnishes can be applied directly into the periodontal pocket. BioC is milder to the soft tissue than EC40. Treatment of patients with chronic periodontitis with EC40 resulted in long term reduction of pocket depth and attachment gain, along with suppression of subgingival microbial species (Cosyn et el., 2006; Cosyn, Thesis, 2006).

- Schaeken MJM, Van der Hoeven JS, de Haan P, Lerk CF. Antimicrobial composition with long-term activity. European patent specification, publication number 0 428 520 B1, 1993.
- Tütüncü R, Tuna A, Noack MJ. Effect of two different chlorhexidine varnishes on plaque-indices and lactobacillus counts. J Dent Res 78: 334, 1999.
- Fischer J. Die Unterdrückung der Mutans Streptokokken im Speichel durch Auftragen des Chlorhexidinzahnlackes EC40 mit unterschiedlichen Applikationsmethoden. Thesis, Universität Witten/Herdecke, 2001.
- Cosyn J, Wyn I, De Rouck T, Sabzevar MM. Long-term clinical effects of a chlorhexidine varnish implemented treatment strategy for chronic periodontitis. J Periodontol 77: 406-415, 2006.

Similarities and differences between BioC and EC40

- BioC and EC40 are concentrated chlorhexidine varnishes, both exhibiting a specific action against mutans streptococci.
- EC40 has the highest concentration of chlorhexidine, and the strongest effect against mutans streptococci.
- BioC is delivered in handy plastic syringes. EC40 is delivered in glass ampoules (carpules)
- BioC tasts less bitter than EC40, and is more suitable for the treatment of small children.
- BioC is milder for the soft tissues and can be used in periodontal pockets.
- In case of high caries activity, it is advisable to repeat the treatment with BioC or EC40, for instance monthly.

Table 1 »

Treatment with BioC and EC40
• Blow teeth dry; in principle plaque does not have to be removed. • Apply a thin layer of BioC or EC40 using the (carpule) syringe; avoid excess of varnish. • Treat the locations for which caries has a predilection. It is not necessary to treat all surfaces. • The varnish should be left on the teeth after application for at least 5 - 10 minutes. Thereafter, it may be removed by the dentist, or left in place. • The patient can brush off the varnish at home. • BioC and EC40 can be applied directly into the periodontal pocket.

Treatment with BioC and EC40

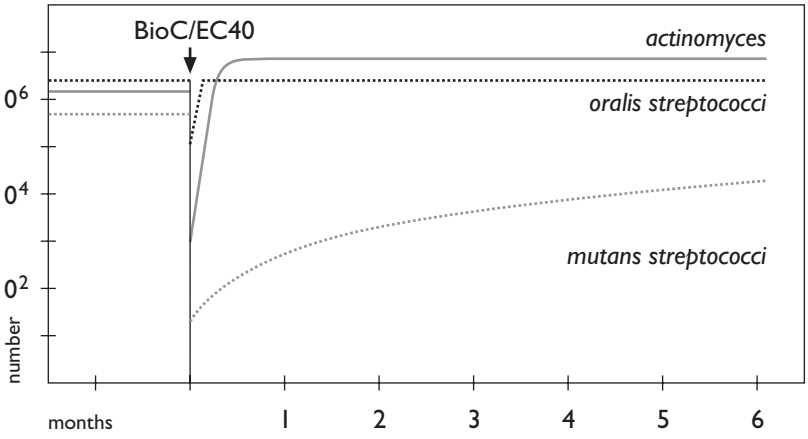
The most important aspects of treatment with BioC and EC40 are summarised in *Table 1*. The varnishes are applied by a dentist or dental hygienist. The tooth surface is first blown dry, after which EC40 can be applied with the aid of a (carpule) syringe. It is not necessary to remove the plaque beforehand. Use a small amount of material; a thin layer of BioC or EC40 is sufficient to produce a good effect. Excess BioC or EC40 leads to unnecessary contact with the gums which may result in irritation of the marginal gingiva. In particular sites of the dentition for which caries has a predilection must be treated. After a contact of 5 - 10 minutes the varnishes may be removed by the dentist, but the varnish may also be left in place. If desired, the patient can brush it off at home.

Mode of action of BioC and EC40

Figure 2 »

Effects of BioC and EC40 on the oral microflora

Oralis streptococci soon recover after treatment. Actinomyces return more slowly, while mutans streptococci remain suppressed for a long period of time.



The effects of BioC and EC40 can best be illustrated by the changes in the microbial composition of the plaque that occur following their application *(Figure 2)*. Firstly, BioC and EC40 kill all bacteria on the treated surface of the teeth. After a few hours, the surface will again be populated by bacteria which adhere from the saliva and start to multiply. Species of bacteria which are least sensitive to chlorhexidine have the best chance in this phase. These bacteria are, in particular, the group comprising **oralis streptococci**, including *S. sanguis, S. oralis* and *S. gordonii (see also Table 3)*. Within a few days these bacteria have fully recovered from the EC40 treatment. Another important species in the supragingival dental plaque, *Actinomyces naeslundii*, is more sensitive to chlorhexidine and returns only after one to two weeks. *Actinomyces naeslundii* often reaches higher numbers in the dental plaque after BioC and EC40 application than before *(Figure 2)*.

Table 2 »

MIC50 for chlorhexidine (mmol/l)	
Streptococcus mutans	0.8
Streptococcus sobrinus	2.0
Streptococcus sanguis	5.0
Actinomyces naeslundii	1.6
Lactobacillus casei	3.2
Actinobacillus actinomycetemcomitans	3.2
Fusobacterium nucleatum	3.2
Veillonella parvula	1.6

MIC50: minimum inhibitory concentration for 50% of the tested strains

In contrast to the oralis streptococci and the actinomyces, the **mutans streptococci** recover only very slowly from the EC40 treatment. There are various reasons for this:

- the mutans streptococci are **more sensitive to chlorhexidine** than the majority of other plaque bacteria *(see also Table 2)*,
- the mutans streptococci are **less competitive** than many other oral streptococci because they:
- are not able to liberate sugars from the **glycoproteins in the saliva as a source of nutrients** but are dependent for their growth on sugars from the food. The oralis streptococci and the actinomyces do use these glycoproteins and are thus ensured of a continually present source of nutrients.

The selective suppression of the mutans streptococci is thus caused by shifts in the microflora as a consequence of the chlorhexidine treatment. These shifts involve other streptococci and actinomyces species taking the place of the mutans streptococci in the ecosystem. The long-term reduction in the number of mutans streptococci in the plaque leads to an appreciable reduction in caries.

It is important to note that chlorhexidine mouthrinses will generally not result in long-term suppression of mutans streptococci.

- Schaeken MJM, van der Hoeven JS, Hendriks JCM. Effects of varnishes containing chlorhexidine on the human dental plaque flora. J Dent Res 68: 1786-1789, 1989.
- Van der Hoeven JS, Schaeken MJM. Streptococci and actinomyces inhibit regrowth of Streptococcus mutans on gnotobiotic rat molar teeth after chlorhexidine varnish treatment. Caries Res 29: 159-162, 1995.

Table 3 »

Clinical trials with EC40 chlorhexidine varnish			
	N	Type of trial	% caries reduction
Schaeken (1991)	20	Root surfaces	65
Boezeman (1994)	22	Orthodontic patients	63
Fennis-le (1998)	25	School children	35*
Gruythuysen (1998)	97	School children	73
Du (2006)	334	Preschool children	37

** Caries reduction in addition to that achieved by six-monthly fluoride applications.*

Caries reduction in man

All clinical trials carried out to date show that EC40 has a caries-inhibiting action *(Table 3)*.

- The study by Schaeken et al. was carried out on adult parodontitis patients with numerous exposed tooth roots. EC40 was applied every three months. The reduction in caries after one year, expressed as the reduction in the number of new tooth root lesions, was 55%. If the hardening of existing lesions in these patients was also taken into account, the reduction was 85%.
- The experiment carried out by Boezeman et al. related to children between 10 and 19 years old who had received orthodontic treatment. EC40 was applied around the brackets during the check-ups every 4 - 6 weeks. At the end of the treatment the number of initial lesions was determined. The EC40 treatment was effective even in the highly cariogenic environment around the brackets.
- The Fennis-le trial was carried out in collaboration with the Stichting Jeugdtandverzorging Oss (Oss Youth Dental Care Foundation). A group of children received treatment with EC40 in addition to the standard treatment, which also included six monthly fluoride application. After three years it was found that EC40 still had an effect (35% caries reduction) over and above that of the fluoride applications. This is in line with the theory that the mechanisms of action of fluoride and EC40 are different.
- In the clinical trial carried out by Gruythuysen et al. in Surinam, children received treatment with EC40 every six months over a period of 2.5 years. A neutral (non-active) gel was applied in the control group. The results after one year showed an appreciable reduction of caries in the molars in the EC40 group. Unfortunately, the children that were recruited for the experiment were in need of dental treatment and often had open carious lesions. Their dentition was put in order not until the second and third year of the study. This has ruined the experiment, so that no reliable data can be given after the first year.
- Du et al. studied the effects of EC40 application every six months on caries development in pre-school children. The 2-year mean caries increments showed a significant reduction of 37% of dmfs-molar in children treated with EC40 compared with children treated with placebo varnish. No side effects were reported. Since the placebo varnish, consisting of sandarac in ethanol, has considerable anti-microbial activity, the caries reduction reported in the EC40 group is a conservative estimate.

- Boezeman PM, Kuijpers-Jagtman A, Schaeken MJM, van der Hoeven JS. Suppression of mutans streptococci and caries prevention in orthodontic patients by application of EC40 chlorhexidine tooth varnish. University of Nijmegen, Internal Report, 1994.
- Boezeman PM, Schaeken MJM. Cariëspreventie tijdens orthodontische behandeling. Het Tandheelkundig Jaar 1996: 84-94.
- Fennis-le YL, Verdonschot EH, Burgersdijk RCW, König KG, van 't Hof MA. Effect of 6-monthly applications of chlorhexidine varnish on incidence of occlusal caries in permanent molars: a 3-year study. J Dent 26: 233-238, 1998.
- Gruythuysen R, van Amerongen WE. Preliminary report of a clinical trial in Surinam.
- Schaeken MJM, Keltjens HMAM, van der Hoeven JS. Effect of fluoride and chlorhexidine on the microflora of dental root surfaces and progression of root-surface caries. J Dent Res 70: 150-153, 1991.
- Du MQ, Tai BJ, Jiang H, Lo ECM, Fan MW, Bian Z. A two-year randomized clinical trial of chlorhexidine varnishin Chinese preschool children. J Dent Res 85: 557-559, 2006.

Interaction of BioC and EC40 with fluoride

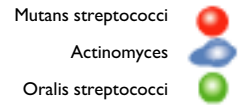
Here a distinction must be made between the interactions of chlorhexidine with the free fluoride ion, for example from sodium fluoride, and the interactions with monofluorophosphate (MFP). F is covalently bonded in monofluorophosphate and the substance reacts as a phosphate.

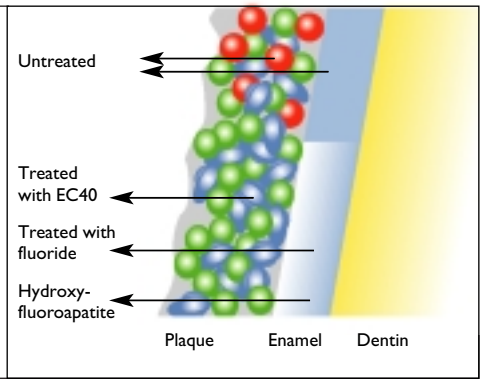
Chlorhexidine is basic and forms salts with negative ions. Thus, the difluoride salt CHX.2F is formed with fluoride. The solubility of this salt is approximately 5 g/l, i.e. 20 mmol/l, corresponding to a concentration of approximately 400 ppm F free fluoride in solution.

Chlorhexidine reacts in the same way with monofluorophosphate (MFP) to give the salts CHX.PO3F and the difluorophosphate: CHX.2PO3F. The solubility of these salts in water is less than that of CHX.2F. As a result, in the presence of chlorhexidine, MFP is bound in salts of low solubility. The solubility of CHX.2PO3F is 0.4 g/l or approximately 0.6 mmol/l. An equivalent quantity of fluoride can be released from this, i.e. 1.2 mmol/l or 24 ppm F.

Figure 3 »

The preventive actions of BioC, EC40 and fluoride. BioC and EC40 suppress the mutans streptococci in the dental plaque. Fluoride catalyses the remineralisation by formation of hydroxyfluoroapatite. Chlorhexidine inhibits the cariogenic mutans streptococci.





It is therefore plausible that CHX and fluoride are compatible *(Figure 2)*. In fact, clinical trials show that combinations of CHX with fluoride in a mouthwash, in toothpaste and in a gel (Luoma et al., 1978; Dolles and Gjermo, 1980, Keltjens et al., 1990) inhibit caries very effectively and better than fluoride alone.

The combination of CHX with monofluorophosphate in a product presents technical problems because sparingly soluble CHX salts with monofluorophosphate are formed, as a result of which, probably, deactivation of fluoride occurs. (Senior, 1973; Barkvoll et al., 1988).

On the basis of the above it appears worthwhile to formulate a combination preparation of concentrated chlorhexidine varnish with sodium fluoride.

- Barkvoll P, Rölla G, Bellagamba S. Interaction between chlorhexidine digluconate and sodium monofluorophosphate in vitro. Scand J Dent Res 96: 30-33, 1988.
- Dolles OK, Gjermo P. Caries increment and gingival status during two years' use of chlorhexidine- and fluoride-containing dentifrices. Scand J Dent Res 88: 22-27, 1980.
- Keltjens HMAM, Schaeken MJM, van der Hoeven JS, Hendriks JCM. Caries control in overdenture patients: 18-month evaluation on fluoride and chlorhexidine therapies. Caries Res 24: 371-375, 1990.
- Luoma H, Murtomaa H, Nuuja T, Nyman A, Nummikoski J, Ainamo J et al. A simultaneous reduction of caries and gingivitis in a group of schoolchildren receiving chlorhexidine fluoride applications. Caries Res 12: 290-298, 1978.
- Senior N. Some observations on the formulation and properties of chlorhexidine. J Soc Cosmet Chem 24: 259-278, 1973.

The effect of sugar consumption on the action of chlorhexidine varnish

The mutans streptococci are dependent for their growth on carbohydrates from the food. The question can be posed as to whether sugar (sucrose) has a greater effect on the growth and accumulation of mutans streptococci than do other types of carbohydrates, such as glucose and starch. Animal experiments have shown that, when consumed very frequently over prolonged periods, sugar accelerated the accumulation of mutans streptococci. Moderate consumption of sugar, for example 3 to 4 times a day, has little additional effect on the mutans streptococci.

What this means in practice is that there is no reduction in the action of BioC and EC40 in the case of a moderate consumption of sugar by the patient.

- Van der Hoeven. Rekolonisation von Mutans Streptokokken aufgrund von Saccharosekonsum nach deren Suppression mit Chlorhexidinlack. (Recolonisation of mutans streptococci by reason of sucrose consumption following the suppression thereof with chlorhexidine varnish) Deutsch Zahnärztliches Zeitschrift, 54: 623- 626, 1999.

Chlorhexidine varnishes and periodontitis

Concentrated chlorhexidine varnishes such as EC40 and BioC can also be used for application in the periodontal pocket. The clinical effects of EC40 application as an adjunct to scaling and root planning (SRP) were studied in patients with chronic periodontitis. The combination therapy with EC40 resulted in additional reduction of pocket depth and attachment gain compared with SRP alone. Monitoring of some subgingival bacterial species showed long-term suppression, in particular of *Tannerella forsythensis* and *Treponema denticola*, following EC40 application.

- Cosyn J, Wyn I, De Rouck T, Sabzevar MM. A chlorhexidine varnish implemented treatment strategy for chronic periodontitis: short-term clinical observations. J Clin Periodontol 32: 750-756, 2005.
- Cosyn J, Wyn I, De Rouck T, Sabzevar MM. Long-term clinical effects of a chlorhexidine implemented treatment strategy for chronic periodontitis. J Periodontol 77: 406-415, 2006.

Sensitivity to CHX and the development of resistance to CHX

Chlorhexidine has an bactericidal effect against Gram-positive and Gram-negative oral bacteria. *(Table 3)*. The sensitivity, expressed as MIC50 values (minimum inhibitory concentration for 50% of the tested strains of a specific species), of *Actinomyces, Streptococcus, Lactobacillus, Actinobacillus, Fusobacterium* and *Veillonella* strains is of the order of <1 - 5 mmol/l chlorhexidine. The differences in sensitivity between the species within the said genera are relatively small. *S. mutans* is more sensitive to CHX than other dominant species of bacteria of the supragingival dental plaque, such as *S. sanguis* and *A. naeslundii*.

Regular use of chlorhexidine does not lead to overgrowth by undesired microflora, such as yeasts, in the mouth. Rinsing with chlorhexidine solution over a prolonged period gives rise to virtually no changes in the sensitivity of the oral flora to chlorhexidine. There are a few indications that *S. sanguis* becomes somewhat less sensitive to chlorhexidine.

- Baker PJ, Coburn RA, Genco RJ, Evans RT. Structural determinants of activity of chlorhexidine and alkyl bis-biguanides against the human oral flora. J Dent Res 66:1099-1106, 1987.
- Mikkelsen L, Börglum Jensen S, Löe H. Susceptibility to chlorhexidine of plaque streptococci after two years oral chlorhexidine hygiene. J Periodont Res 17:366-373, 1982.

Table 4 »

Chlorhexidine loading

	Conc. CHX	Dose	Total CHX	Retention of CHX
Mouthwash	0.2%	10 ml	20 mg	7 mg1
Gel	1%	8 g	80 mg	35 mg2
EC40	35%	0.25 ml	90 mg	20 mg3
BioC	20%	0.25 ml	50 mg	10 mg3

1 Bonesvoll P, Lökken P, Rölla G, Paus PN. Retention of chlorhexidine in the human oral cavity after mouth rinses. Arch Oral Biol 19: 209-212, 1974.

2 Bonesvoll P. Retention and plaque-inhibiting effect in man of chlorhexidine after multiple mouthrinses and retention and release of chlorhexidine after toothbrushing with a chlorhexidine gel. Arch Oral Biol 23:295-300, 1978.

3 Estimated quantity of chlorhexidine that remains behind in the mouth after removal of varnish by brushing the teeth.

Chlorhexidine loading

Table 4 gives a summary of the chlorhexidine loading for single use of various chlorhexidine preparations. On average 90 mg chlorhexidine is introduced into the mouth during a treatment with EC40 (the amount ranges from about 50 - 150 mg when 1 carpule is used for 3 - 10 patients). This chlorhexidine is in the varnish and will slowly be liberated therefrom by dissolving in the saliva. The half life for the liberation of CHX from the varnish applied is 12 hours (Schaeken and de Haan, 1989).
The chlorhexidine loading is appreciably reduced (to about 10 - 20 mg) if the varnish is removed by the dentist or brushed off by the patient. A similar estimate can be made for BioC.
For comparison, the chlorhexidine dose when rinsing with a 0.2% solution is 20 mg. About 6 mg of this remains behind adsorbed in the mouth. Daily rinsing with chlorhexidine solution rapidly leads to a much higher loading with chlorhexidine than does a single application of EC40. The loading is the highest when a 1% chlorhexidine gel is used, in particular because the gel application has to be repeated several times within a short time.

As a consequence of the low degree of absorption in the gastrointestinal tract, the acute oral toxicity of chlorhexidine is low. The LD50 is 2 g/kg body weight. Long-term use of 0.05% chlorhexidine diacetate (the chlorhexidine salt used in EC40) in the food has no demonstrable adverse effects on monkeys and rats.

Humans who consumed 2 g chlorhexidine per day for a period of one week showed no adverse consequences, such as problems with the intestinal flora.

- Schaeken MJM, de Haan P. Effects of sustained-release chlorhexidine acetate on the human dental plaque flora. J Dent Res 68: 119-123, 1989.
- Senior N. Some observations on the formulation and properties of chlorhexidine. J Soc Cosmet Chem 24: 259-278, 1973.

Retention and absorption of chlorhexidine

Chlorhexidine (CHX) is strongly adsorbed at the oral mucosa and the surfaces of the teeth. When mouthwashes and gels are used, approximately 30% of the chlorhexidine in the mouthwash remains behind in the mouth. The bound CHX is released in the course of a few hours.

The absorption and elimination have been studied using radioactively labelled CHX. An oral dose of chlorhexidine is eliminated with a half life of four days. 90% of the material applied is eliminated within 72 hours, virtually completely in the faeces. Absorption in the gastrointestinal tract is very low and little chlorhexidine passes into the urine. Degradation products of chlorhexidine, such as p-chloroaniline, are not found in the urine. There is some retention of chlorhexidine in the liver. The substance is easily extractable from this and is thus not covalently bonded to proteins.

- Bonesvoll P, Lökken P, Rölla G, Paus PN: Retention of chlorhexidine in the human oral cavity after mouth rinses. Arch oral Biol 19: 209-212, 1974.
- Winrow MJ: Metabolic studies with radiolabelled chlorhexidine in animals and man. J Periodont Res 8: Suppl 12: 45-48, 1973.

Table 5 »

Side effects	BioC EC40	CHX rinsing
Discoloration of mucosa/teeth	-	+++
Local irritation/desquamation of mucosa	+/-	-
Swelling and desquamation of mucosa	vr	vr
Swelling of parotid gland	vr	vr

vr : very rare, estimated frequency 1 in 25,000.

Side effects of BioC and EC40

The most common side effects of chlorhexidine are listed in *Table 5*. The known brown discoloration of the teeth and the mucosa occurs in particular in the case of frequent use of chlorhexidine. A single application of BioC or EC40 therefore does not lead to discolorations. Slight desquamation of the oral mucosa, in particular the border of the gingiva, can arise on prolonged contact with EC40, but has sofar not been observed with BioC.

Swelling of the parotid gland is a rare side effect of BioC and EC40. The swelling disappears spontaneously after a few days. Hypersensitivity to chlorhexidine with swelling and redness of the oral mucosa is likewise a rare phenomenon. The swelling disappears spontaneously in the course of a few days. On the basis of the side effects reported to us, the estimated frequency of the occurrence of swelling of the parotid gland is 1 in 100,000 and that of swelling of the oral mucosa 1 in 25,000. This is in agreement with data from the literature.

- Seymour RA, Meechan JG, Walton JG. Adverse drug reactions in dentistry. Oxford University Press, Oxford, pp.68-71, 1996.