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MINIREVIEW

N-Chloramines, a Promising Class of Well-Tolerated Topical Anti-Infectives

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Antibiotic resistance is a growing public health crisis. To address the development of bacterial resistance, the use of antibiotics has to be minimized for nonsystemic applications in humans, as well as in animals and plants. Possible substitutes with low potential for developing resistance are active chlorine compounds that have been in clinical use for over 180 years. These agents are characterized by pronounced differences in their chlorinating and/or oxidizing activity, with hypochlorous acid (HOCl) as the strongest and organic chloramines as the weakest members. Bacterial killing in clinical practice is often associated with unwanted side effects such as chlorine consumption, tissue irritation, and pain, increasing proportionally with the chlorinating/oxidizing potency. Since the chloramines are able to effectively kill pathogens (bacteria, fungi, viruses, protozoa), their application as anti-infectives is advisable, all the more so as they exhibit additional beneficial properties such as destruction of toxins, degradation of biofilms, and anticoagulative and anti-inflammatory activities. Within the ample field of chloramines, the stable *N*-chloro derivatives of ß-aminosulfonic acids are most therapeutically advanced. Being available as sodium salts, they distinguish themselves by good solubility and absence of smell. Important representatives are *N*-chlorotaurine, a natural compound occurring in the human immune system, and novel mono- and dichloro derivatives of dimethyltaurine, which feature improved stability.

One of the most impressive innovations in medicine was the discovery of antibiotics in the foregoing century. Applied systemically, they enabled the successful treatment of diseases that often end lethally without antibiotics. Beside their undoubted merits, they have a serious drawback, as pathogens can become resistant to most antibiotics, with their therapeutic value being extensively reduced or even lost, particularly in cases of overprescription. To address the development of resistance, those applications where antibiotics are used topically have to be minimized. This also concerns fields that are not directly related to human health, such as combating diseases of animals (mastitis of cows) or plants (fire blight). In both cases, residues of antibiotics can linger in the environment and find their way into humans, allowing bacteria to build resistance.

To address this situation, agents capable of inactivating pathogens without inducing resistance were screened. A possible group of candidates are halogens and oxidizing halogen compounds, which indeed cannot be applied systemically, where they lose their activity because of immediate reduction by sulfur compounds (e.g., >N-Cl + 2R-SH → R-SS-R + >N-H + H^+ + Cl^-) (1). A topical application, however, is possible, and resistance problems have never been observed.

The goal of this paper is to characterize this large class of compounds in view of their suitability as anti-infectives. This needs a detailed study of intrinsic properties such as bactericidal activity, mode of action, tissue irritation, and consumption effects.

ACTIVE HALOGEN COMPOUNDS

The halogens, mainly chlorine and iodine, have a long tradition as anti-infectives (1, 2), while bromine has been of only secondary importance until now, as seen by the number of publications. Chlorine and iodine behave very differently. Chlorine affords stable O-Cl and N-Cl compounds, the so-called active chlorine compounds, which act as germicidal agents based on their oxidizing qualities. In the case of iodine, however, the analogous O-I and N-I compounds are not stable in an aqueous system and therefore not practically useful (3).

Active chlorine compounds. Chlorine gas (Cl_2) as a very strong oxidant reacts immediately with water, forming hypochlorous acid, HOCl (equation 1), which, as the most powerful active chlorine compound, is relatively stable under biological pH conditions.

$$Cl_2 + H_2O \leftrightarrow HOCl + H^+ + Cl^- \quad (1)$$

From HOCl derive all active chlorine compounds according to equations 2 to 4.

$$HOCl \leftrightarrow OCl^- + H^+ \quad (2)$$

$$HOCl + >N\text{-}H \rightarrow >N\text{-}Cl + H_2O \quad (3)$$

$$HOCl + R\text{-}O\text{-}H \rightarrow R\text{-}O\text{-}Cl + H_2O \quad (4)$$

The species OCl^- forms the anion of salts such as NaOCl or $Ca(ClO)_2$ (sodium hypochlorite, chlorinated lime), while the symbol >N-Cl includes all nitrogen-chlorine compounds. The latter can be divided into chloramines, with a saturated carbon atom adjacent to the N-Cl function, -CH_2-NCl-, and chloramides or chlorimides, with one and two carbonyls next to N-Cl, i.e., -CO-NCl- and -CO-NCl-CO-, respectively. The chloramines and the chloramides can also be substituted by a second chlorine atom, forming *N*-dichloro compounds with the structure element -NCl_2 (4, 5).

Historical excerpt. Soon (only 15 years) after the discovery of chlorine by Scheele (1774), the hypochlorites were described for the first time by Berthollet (1789), and it did not take long until their germicidal properties were detected. Already in 1825, the use

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of calcium hypochlorite for general sanitation was reported by Labarraque (6). He also reported success in treatment of ulcers and burns covered with dressings with dilute hypochlorite solution, which essentially signifies the first report about the anti-infective use of an active chlorine compound (6). The combat of childbed fever by Semmelweis (1847, 1861) (7) employing lime of chlorine was then in reality the first triumph of this class of compounds. In 1915, Dakin introduced a solution of alkaline 0.5% sodium hypochlorite for disinfection of open wounds in World War I (8). One year later, Dakin and Cohen reported the treatment of infected wounds by chloramine T (*N*-chloro-4-methylbenzenesulfonamide sodium), which was favored versus hypochlorite because of less irritation and chlorine consumption and higher stability (9). The authors already recognized that the high alkali content of hypochlorite was the main reason for strong irritation. A completely new approach succeeded when a formulation containing commercial bleaching powder ($CaOCl_2$) and boric acid became available, which, dissolved in water, gave a feeble alkaline antiseptic solution that was named Eusol, whose active principle was identified as free hypochlorous acid (HOCl). The authors stressed the striking fact that it is nontoxic to tissues but highly destructive to bacteria (10). HOCl solutions are still of interest, as can be derived from a recent study on the treatment of chronic venous leg ulcers (11).

A completely new anti-infective concept was the introduction of a chloramine in the form of the natural compound *N*-chlorotaurine (NCT), which was successfully used in several clinical studies (12–21). In a comparative trial on chronic leg ulcers, NCT showed the same efficacy as chloramine T but induced significantly less pain (17). This has led to successful further use under controlled conditions in this application in our university hospital. Scores of inflammation and the time to healing were also significantly improved by NCT compared to a standard therapy in treatment of external otitis (18) and to placebo in treatment of epidemic keratoconjunctivitis (21, 22). Inspired by the usefulness of NCT, dimethylated derivatives of NCT (*N*-chloro-2,2-dimethyltaurine [DM-NCT] [23–25] and *N*,*N*-dichloro-2,2-dimethyltaurine [DM-NDCT] [5, 26]), which are analogs of natural compounds and attract attention by improved stability, have been introduced.

MECHANISM OF BACTERIAL KILLING BY ACTIVE CHLORINE COMPOUNDS

Approach. The interaction of a bactericidal agent with the bacterium essentially depends on the circumstances of the approach. Since bacteria are negatively charged, the polarity of the agent plays an important role. Three alternatives are conceivable:

- Agents that are present as anions, such as the sodium salts chloramine-T (CAT), NCT, DM-NCT, and DM-NDCT.
- Neutral molecules, such as HOCl, NH_2Cl, and ClO_2 and the protonated forms of NCT and their dimethylated derivatives (which as a whole are neutral molecules, i.e., $ClH_2N^+ \ldots SO_3^-$).
- Positively charged agents, such as protonated monochloramine, NH_3Cl^+ (relevant only at pH < 6).

It is evident that the ease of approach is better for neutral and best for positively charged agents, while it is worst for anions, which are subject to Coulomb repulsion.

Formation of a chlorine cover. The first attack of an active chlorine compound concerns chlorination of the external protein matrix of the bacterium, i.e., formation of a chlorine cover made up of covalent N-Cl bonds (27, 28). It was shown that a moderate chlorine cover does not impair the viability of bacteria, a result that was judged as evidence for the importance of penetration (27) (see below).

Compact chlorine covers, on the other hand, e.g., attached by a very strongly oxidizing agent like dichloroisocyanuric acid (DCI), were 38-fold stronger than when attached by the weakly oxidizing chloramine NCT and caused cell leakage with immediate killing (27).

Penetration. Coincidentally with superficial chlorination, penetration into intact pathogens and body cells also takes place, resulting in the initiation of the irreversible transformation (destruction) of vitally important constituents, mainly S-H functions (see below) (29–31). It is widely accepted knowledge that penetration is favored for noncharged agents with low bulk (32). But there also exist examples where this concept seems to be upset. The comparison of the noncharged agents monochloramine (NH_2Cl; molecular weight, 51.5) and molecular iodine (I_2; molecular weight, 254) shows a higher bactericidal activity of iodine against Gram-positive bacteria, notwithstanding a 5-fold-higher molecular bulk (W. Gottardi, R. Arnitz, and M. Nagl, unpublished results). A conceivable reason is a difference in lipophilicity, which obviously plays an important role in the penetration rate. This feature can also be considered for charged agents such as NCT (molecular weight, 181.6) and its dimethyl analog, DM-NCT (molecular weight, 209.6), where the latter is significantly more bactericidal against both Gram-positive and Gram-negative bacteria in spite of its higher bulk (M. Nagl, unpublished results).

Inactivation of vital sites. If the agent has penetrated the bacterial cell, disintegration reactions occur by chlorination (equations 5 and 6) and/or oxidation (equations 7a to f). This is a mere chemical occurrence, which has to be seen in a different way than leakage, which first of all is a mechanical (physical) process that speeds up the destruction of critical enzymes and structures essential for cell survival.

The interaction of active chlorine compounds (X-Cl) with proteinaceous material, which leads to chlorine consumption, can be reduced to the same three main reactions (equations 5 to 7) (31, 33–37):

- Transchlorination

$$\text{R-NH}_2 + \text{X-Cl} \leftrightarrow \text{R-NHCl} + \text{X-H} \quad (5)$$

$$\text{R} = \text{H, -CH(R}''\text{)-COOH; R}'' = \text{alkyl}$$

$$\text{X} = \text{-O- , >N-}$$

- Chlorination of aromatic compounds

$$\text{Ar-H} + \text{X-Cl} \rightarrow \text{Ar-Cl} + \text{X-H} \quad (6)$$

$$\text{Ar-H} = \text{aromatic hydrogen (tyrosine, histidine)}$$

- Oxidation of sulfur compounds

$$2\text{R}'\text{-S-H} + \text{X-Cl} \rightarrow \text{R}'\text{-SS-R}' + \text{X-H} + \text{H}^+ + \text{Cl}^- \quad (7)$$

$$\text{R}'\text{-S-H} + \text{X-Cl} + \text{H}_2\text{O} \rightarrow \text{R}'\text{-SOH} + \text{X-H} + \text{H}^+ + \text{Cl}^-$$

$$\text{R}'\text{-SOH} + \text{X-Cl} + \text{H}_2\text{O} \rightarrow \text{R}'\text{-SO}_2\text{H} + \text{X-H} + \text{H}^+ + \text{Cl}^-$$

$$\text{R}'\text{-SO}_2\text{H} + \text{X-Cl} + \text{H}_2\text{O} \rightarrow \text{R}'\text{-SO}_3\text{H} + \text{X-H} + \text{H}^+ + \text{Cl}^-$$

$$\text{R}'\text{-S-CH}_3 + \text{X-Cl} + \text{H}_2\text{O} \rightarrow \text{R}'\text{-SO-CH}_3 + \text{X-H} + \text{H}^+ + \text{Cl}^-$$

$$\text{R}'\text{-SS-R}' + 2\,\text{X-Cl} + 2\text{H}_2\text{O} \rightarrow 2\text{R}'\text{-SOH} + 2\,\text{X-H} + 2\text{H}^+ + 2\text{Cl}^-$$

$$\text{R}' = \text{-CH}_2\text{-CH(NH}_2\text{)-COOH (cysteine, methionine)}$$

The transchlorination reaction of equation 5 is reversible;

therefore, it comes to an equilibrium, and oxidation capacity, c(Ox) = [>N-Cl] + [R-NHCl], is retained. The reactions of equations 6 and 7, by contrast, are irreversible and c(Ox) is completely lost.

Loss of c(Ox) by transchlorination. Notwithstanding the postulated retention of c(Ox) in the case of transchlorination (equation 5), it can decrease rapidly if the reaction product consists of *N*-chloro derivatives of α-aminocarbonic acids such as *N*-chloroalanine or chlorinated peptides, which are not stable (38, 39). A prerequisite for this instability is the structural element ClHN-CH(R)-CO-, which is transformed by a spontaneous HCl elimination to an imine (equation 8), which forms an aldehyde and ammonia with water in the sequel (equation 9).

$$\mathrm{ClHN\text{-}CH(R)\text{-}CO\text{-}R' \rightarrow HN{=}C(R)\text{-}CO\text{-}R' + H^+ + Cl^-} \quad (8)$$

$$\mathrm{HN{=}C(R)\text{-}CO\text{-}R' + H_2O \rightarrow O{=}C(R)\text{-}CO\text{-}R' + NH_3} \quad (9)$$

R=H, alkyl; R′ = OH, peptide rest

The reactions of equations 8 and 9 become significantly less important with *N*-chloro-β-aminosulfonic acids like NCT, and they are absent with the new synthetic NCT derivatives DM-NCT and DM-NDCT, which lack a C-H bond next to the ClHN- (Cl_2N-) function, making elimination according to equation 8 impossible.

The reactions of equations 5 to 7, i.e., those which in the end are responsible for irreversible and lethal transformations (killing), differ in their rates. While the oxidation of sulfur compounds (equation 7) is generally complete within seconds (35, 37), the reaction of equation 6, standing for an aromatic substitution reaction, proceeds substantially slower. The equilibrium of transchlorination (equation 5), on the other hand, settles within minutes, e.g., in 10 to 15 min in the case of the reaction NH_4Cl + NCT ↔ NH_2Cl + taurine (32). These qualities can be attributed to differences in the susceptibilities of the particular functions for oxidation (chlorination).

Chemical reactivity of active chlorine compounds. Among active chlorine compounds, the following order of oxidizing (chlorinating) potency can be established: HOCl > *N*-chlorimides (e.g., chloroisocyanuric acids) > monochloramine (NH_2Cl) > *N*-chloramides (e.g., chloramine T) > *N*,*N*-dichloramines (e.g., *N*,*N*-dichloro-dimethyltaurine) ≈ *N*-chloramines (e.g., NCT, *N*-chloro-dimethyltaurine).

The found order, which correlates largely with bactericidal data, was estimated from the ability to build up chlorine covers on skin (40) and bacterial surfaces (27) by assessing their strength and rate of formation. A similar order could be deduced from differences in the loss of oxidation capacity assessed by chlorine consumption experiments (41).

The chlorine covers are the result of the reaction of equation 5, while the consumption effects relate directly to the reactions of equations 6 and 7 and indirectly to the degradation formulated by equations 8 and 9. The reactions of equation 7, in addition, are of special importance because thiols (cysteine) and thioethers (methionine) are extremely sensitive to oxidation, therefore reacting very fast even with weak oxidants such as chloramines (35). Many vitally important substrates, such as enzymes, within the cell contain cysteine and methionine components. This is why fast killing occurs also with chloramines. This feature is important for understanding their potential as potent anti-infectives with minimal side effects.

The influence of pH on the reactivity. Discussing this issue, one has to differentiate between (i) the actual agents and (ii) their target, i.e., bacterial and tissue cells.

(i) Most active chlorine compounds undergo reactions in aqueous solution, which can be summarized by the terms dissociation (equation 10), hydrolytic HOCl formation (equation 11), disproportionation (equation 12), protonation (equation 13), and hydrolysis (equation 14).

$$\mathrm{HOCl \leftrightarrow OCl^- + H^+} \quad (10)$$

$$\mathrm{Cl_2HN_3C_3O_3 + H_2O \leftrightarrow ClH_2N_3C_3O_3 + HOCl} \quad (11)$$

$$\mathrm{2ClHNCH_2CH_2SO_3^- + H^+ \leftrightarrow Cl_2NCH_2CH_2SO_3^- + H_3N^+CH_2CH_2SO_3^-} \quad (12)$$

$$\mathrm{NH_2Cl + H^+ \leftrightarrow NH_3Cl^+} \quad (13)$$

$$\mathrm{CH_3\text{-}C_6H_4\text{-}SO_2NCl^- + H_2O \leftrightarrow CH_3\text{-}C_6H_4\text{-}SO_2NHCl + OH^-} \quad (14)$$

The listed examples concern the dissociation of hypochlorous acid (equation 10), the hydrolytic HOCl formation from dichloroisocyanuric acid (equation 11), the disproportionation of NCT (equation 12), the protonation of chloramine (equation 13), and the hydrolysis of chloramine T (equation 14).

It is evident that these reactions are highly controlled by the prevailing pH and, what is more, that there is no longer a single agent present, but two, three, or even more measurable species, which differ in their intrinsic activities. A well-known example is the influence of the pH on the bactericidal activity of HOCl (equation 10) in a neutral milieu. Already small variations of the pH affect the ratio of highly bactericidal HOCl and weakly active OCl^- (see below), which is exactly 1:1 at pH 7.53 (which equals the pKa of HOCl) (1). More complex is the situation with N-Cl compounds, which undergo also the reactions of equations 11 to 13 in measurable proportions in the biologically relevant pH range of 4 to 8. For, e.g., chloramine T, at least five oxidizing components in aqueous solution are discussed: R-NCl^-, R-NHCl, R-NCl_2, HOCl, and OCl^- (R = CH_3-C_6H_4-SO_2) (42). The increased reactivity with acidity is a general occurrence with active chlorine compounds and was reported also for NCT (30, 43) and NH_2Cl (44).

(ii) Since the negative charge of bacterial and superficial tissue cells (which evolves from free carboxylate groups sticking to surface proteins) becomes neutralized if acidity increases, the already-mentioned Coulomb repulsion for negatively charged species is also diminished, effecting an increase of the susceptibility of the attacked living cells to the agents. In other words, the abovementioned pH effect is even further reinforced.

The meaning of reactivity. The most important observable feature of reactivity concerns the reaction rate, which depends on the following three factors:

1. The concentration ratio of agent and target molecule.
2. Susceptibility of the target molecule (e.g., R-S-H, Ar-H) for a defined reaction (e.g., halogenation, oxidation).
3. The specific reactivity of the agent (e.g., HOCl, NCT) with a delimited target. This can be a single compound (e.g., R-NH_2, Ar-H, R-S-H, CH_3-S-R) or proteinaceous substrates representing mixtures of all oxidizable sites, respectively. As pointed out in the foregoing paragraph, specific reactivity is also influenced by the prevailing pH.

While factor 1 concerns a universally valid principle, it is clear that scaling of factors 2 and 3 has to refer to the same reaction and target, respectively.

The following can be stated:

- The susceptibility to oxidation (chlorination) decreases in the order R-SH $\geq$ CH_3-S-R > R-NH_2 > Ar-H compounds.
- The above-quoted rating of active chlorine compounds is, correctly expressed, a combination of three specific reactivities derived from bactericidal activity, formation of chlorine covers, and chlorine consumption. Although referring to diverse phenomena (features), they are showing the same relative order, which allows their summing up under the concept of general reactivity.
- From presently known experimental data, it can be deduced that, in contact with biological (proteinaceous) material, all active chlorine compounds undergo the same fundamental reactions specified by equations 5 to 7 (31, 33–37). The only difference concerns the reaction rate, a measure for reactivity, which affects their applicability in clinical practice.

HOCl, the strongest bactericide. In view of the above-quoted influencing factors, the favorite concerning bactericidal activity might be hypochlorous acid, HOCl, which fulfills the criteria for effective bacterial killing, i.e., no negative charge, low bulk, and high oxidizing potency (1). Being the strongest chlorine-based oxidant feasible in aqueous solution, it is also the most effective bactericide. However, this qualification applies only to washed bacteria, where the amount of biological contamination causing chlorine consumption is drastically reduced.

Nevertheless, disinfection of swimming-pool water with chlorine is an example of how a very strong oxidant such as HOCl can be tolerated by humans if the concentration is accordingly low. As a result of feeding chlorine gas into the pool water, HOCl is formed (see equation 1) and maintained at a very low concentration equivalent to 0.5 to 1.5 mg Cl_2/liter (7.1 to 21.2 μM). Such a permanent maintenance is generally not possible in clinical application of anti-infectives; initially, considerably higher concentrations would be necessary to offset the inevitable chlorine consumption. However, this is all the more connected with tolerability problems concerning such an oxidant as HOCl.

UNWANTED SIDE REACTIONS

Discussing disinfection procedures, not only are the pathogenic microorganisms to be killed of interest but also the treated material. Concerning the application on human body surfaces, one has to distinguish between intact skin and sensitive sites such as eyes, internal body surfaces (mucous membranes), and open wounds. In the case of the eye, a resistant corneal layer protects the underlying sensitive tissue so that unwanted side reactions, e.g., irritation by a too strong oxidant, may be a problem.

However, in the case of internal body surfaces, etc., which involve the standard anti-infective application, the active chlorine compounds interact not only with the very surface of the treated area (mucosa, wounds) but also with its environment (for instance, blood, pus, and secretions). The latter is composed very heterogeneously and consists of solute and corpuscular matter like amino acids, peptides, proteins, and living and dead bacteria. The main goal of the antiseptic is to kill living pathogens. However, this is connected with the unavoidable chlorination of the quoted surfaces and constituents, which becomes manifest in a 3-fold way as tissue irritation, pain (as a result of the latter), and chlorine consumption.

Tissue irritation and pain. Living tissue is very sensitive to the chemical stress active chlorine compounds exert. It is plausible that strongly oxidizing (chlorinating) agents—in analogy to the attack on bacterial cells (chlorine cover)—cause a disruption of body cells located on the tissue surface, a process that can explain the sense of pain these compounds exert, e.g., on crural ulcers (17). The debris of the disrupted cells results in increased chlorine consumption. As long as the agent is present in a sufficient concentration, degradation of the surface steadily proceeds, with the effect that the enduring tissue irritation boosts chlorine consumption in the case of highly active compounds.

Chlorine consumption. Though not as relevant as irritation, this factor has to be considered whenever the anti-infective comes in contact with significant loads of proteinaceous material (e.g., wounds, inflammations). It can provoke a complete loss of oxidation capacity before destruction of pathogens has started. Model experiments with peptone and fetal calf serum revealed the following order of the rate of consumption (45):

$$\text{HOCl} > \text{DCl} > \text{CAT} \approx \text{NH}_2\text{Cl} > \textit{N}\text{-chloramines} \quad (15)$$

Hence, it can be deduced that by using weak oxidants such as *N*-chloramines, the rate of the quoted reactions (equations 5 to 7) can be reduced, which means less irritation and, most relevant, less pain.

CHOOSING SUITABLE CANDIDATES FOR ANTI-INFECTIVE APPLICATION

Since killing of pathogens and the quoted unwanted reactions are founded on the same reactions (see equations 5 to 7), this goal can be reached only by a compromise that reads as "bactericidal activity that is sufficient and tissue irritation that is as low as possible."

Because the inactivation of pathogens should occur as fast as possible, the definition of the term "sufficient" depends on the nature of the tissue to be treated. Comparatively insensitive sites such as intact skin can tolerate the more aggressive agents, while in cases of very delicate mucosa or open wounds with high loads of reducing material, weak oxidants are beneficial because they curtail chlorine consumption and irritation and, with that, also pain. Actually, this has been confirmed by a direct comparison of chloramine T and NCT for treatment of purulent coated crural ulcers (17). While the therapeutic success was the same for both agents, the weak oxidizing NCT was favored by the patients because of less pain (17).

Chloramine-based agents should be preferred for treatment of infected mucosa and open wounds. Notwithstanding their weak oxidizing properties, they quickly deactivate vital thiol groups, ensuring sufficient microbicidal activity. Concomitantly, they ensure minimal irritation and therefore good tolerability. We can assume that nature not unintentionally has installed the chloramine compound NCT as a prominent player in the human defense system (34, 38, 39, 46).

Intrinsic requirements for chloramines as anti-infectives. General requirements for modern anti-infective preparations valid for chloramines as well are good solubility and stability in the aqueous system, absence of unpleasant smell (this implies a negligible vapor pressure), good tolerability, absence of toxic metabolites, and sufficient activity against pathogens (47). These fundamental require-

ments significantly curtail the number of chloramines coming into consideration. Because of their unpleasant smell, the N-Cl derivatives of mere aliphatic amines are not suitable. This applies mainly to representatives with low molecular weight (e.g., methylamine, ethylamine, and others), while compounds with high molecular weight are largely odorless but lack solubility in water.

An important subsection of the organic amines are the amino acids, whose N-Cl derivatives have the advantage of no vapor pressure and excellent solubility in water, based on their ionic structure (e.g., as sodium salt). Among them, the *N*-chloro-α-aminocarbonic acids [ClNH-CH(R)-COOH] drop out because of instability (37, 39) in spite of the advantage of occurring in the human body (34, 48).

The *N*-chloro-ß-aminosulfonic acids [ClHN-CH_2-CH(R)-SO_3H], on the other hand, are very stable and are potential candidates for antiseptic use in practice (49). Examples are NCT (49) and the *N*-monochloro and *N*,*N*-dichloro derivatives of 2,2-dimethyltaurine (DM-NCT, DM-NDCT) (5, 25, 26, 50). As sodium sulfonates, not only the compound itself but also all species originating from hydrolysis, protonation, and disproportionation are well soluble in the whole pH range (5, 26, 33). This is in contrast to other chloramines, e.g., chloramine T, which—as a sodium salt—is well soluble in water at pH $>$ 6, while the only slightly soluble free acid is formed in acidic milieu (see equation 14) (42).

Availability. NCT, DM-NCT, and DM-NDCT are easily accessible and therefore important candidates for practical use. While NCT is a body's own (natural) compound with the disadvantage of slightly reduced stability (33), DM-NCT and DM-NDCT have long-term stability in solution (5, 24, 26) and are analogs of natural compounds. NCT was investigated for nearly 15 years, and its anti-infective usefulness has been confirmed to date by numerous studies (reviewed in reference 49). DM-NCT and DM-NDCT, on the other hand, are new compounds, whose anti-infective properties are currently explored in detail, yielding promising results, which confirm them as equivalent to NCT (23, 25, 50–52). Specifically, DM-NDCT (NVC-422) is active against a broad range of Gram-positive and Gram-negative bacteria, including drug-resistant pathogens (25), without generating resistance in multiple-passage studies (53). DM-NDCT also inactivates adenovirus and other viruses (50). This compound is currently in clinical trials for the treatment of impetigo (23), urinary catheter blockage and encrustation (UCBE), and adenoviral conjunctivitis (54).

NONMICROBICIDAL EFFECTS CAUSED BY CHLORAMINE COMPOUNDS

Recently, the chloramines gained further attraction by the discovery of properties not directly related to the killing of microorganisms, i.e., destruction of toxins and anticoagulant and anti-inflammatory activity. Though elaborated chiefly with NCT and DM-NDCT, they doubtlessly increase the importance of chloramine-based agents in general. With other bactericidal compounds such as membrane-active agents (quats, chlorhexidine, polyhexanide, etc.), all these quoted effects have not been realized by one substance.

Destruction of toxins by active chlorine compounds. Actually, the active chlorine compound NCT has been shown to remove the virulence of *Staphylococcus aureus* and *Streptococcus pyogenes* after sublethal incubation times in the mouse peritonitis model (30, 55). This was connected with a lag of regrowth (30, 55, 56) and with chlorination of the surface of the pathogens (27). Moreover, secretory aspartyl proteinases of *Candida albicans* were downregulated by sublethal concentrations of NCT, and gliotoxin of *Aspergillus fumigatus* was obviously destroyed by this compound (56, 57). Most recently, oxidation and chlorination of Shiga toxin of enterohemorrhagic *Escherichia coli* by NCT at multiple sites were demonstrated, leading to destruction and inactivation of the toxin (58).

Degradation of biofilms. It was shown that NCT exhibits efficacy against *S. aureus* biofilms (D. Coraca-Huber and M. Nagl, unpublished results). This result and the good tissue tolerability observed in previous clinical studies suggest NCT as an irrigation substance for the prevention and treatment of infections after operations, for instance, in orthopedics. DM-NDCT was shown to be highly efficacious against *S. aureus* biofilm in a sheep model of sinusitis (59). The detailed mechanisms of the activity against biofilm are not known presently, though the demonstration that oxidative reactions are responsible is near at hand.

Anticoagulant function. Potentially fatal microbial infections and thrombosis are the two major challenges associated with indwelling medical devices such as catheters. To manage these problems, two agents are necessary, a bactericidal one and an anticoagulant one, the latter, in general, heparin. Therefore, the discovery of the anticoagulant activity of active chlorine compounds (51, 60, 61) represented important progress because it suggests the use of a single agent for both jobs. On the grounds of their low oxidizing potency, *N*-chloramines are especially favored because, in the presence of up to 75% blood, they are not completely consumed at clinically applicable concentrations and are still active and because they do not interact with heparin, which may be used in combination with, e.g., NCT or DM-NDCT (51).

Anti-inflammatory activity. Concentrations of NCT of up to 0.5 mM induce a downregulation of mainly proinflammatory chemokines, cytokines, and enzymes, i.e., prostaglandin E2, tumor necrosis factor α, nitric oxide, interleukins 1ß, 2, 6, 8, and 12, collagenase, and neopterin (reviewed in references 49 and 62 to 64), and NCT (0.5 mM) induces apoptotic cell death after longer incubation times (65). On the other hand, activation of the fifth component of the complement system has been found (66), but, in general, NCT is assumed to contribute to termination of inflammation (62–64). Actually, in a clinical pilot study, NCT was effective in drying of the noninfected outer ear canal after tympanoplasty and did not impair epithelialization (20). Therefore, anti-inflammatory activity could play a role in application of *N*-chloramino acids.

Bacterial killing and chlorine consumption. Comparing the biological activities of oxidizing halogen compounds discloses that killing times exhibit remarkably higher differences than consumption effects. An impressive example concerns NCT and the very reactive hypochlorous acid (HOCl). While the consumption of HOCl is twice as high (45), the bactericidal effect, however, is approximately 10,000-fold higher (51, 67, 68). This astonishing result can be reduced to both the faster penetration of HOCl and its superior oxidizing activity (see above), which causes immediate inactivation of S-H and S-CH_3 functions of vitally essential enzymes.

CONCLUSIONS

The most important value of active chlorine compounds as anti-infectives is that they attack multiple targets in bacteria (29, 50), which is the reason for the absence of the development of resistance (53, 69). It is a typical and fundamental trait of these agents and represents the decisive difference from antibiotics.

Since the human immune system is based to a significant ex-

tent on the myeloperoxidase-catalyzed formation of HOCl and its follow-up products, i.e., *N*-chloro derivatives of amino acids and proteins, application of chloramines (endogenous and synthetic ones) concerns a class of compounds the human body is already accustomed to, suggesting a broad tolerance. The additional beneficial effects, i.e., destruction of toxins, degradation of biofilm, and anticoagulant and anti-inflammatory activity, are further properties that make N-chloramines an attractive class of topical anti-infectives.

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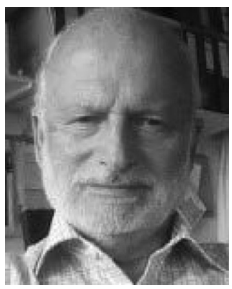

Waldemar Gottardi is a Ph.D. and specialist for halogens and active halogen compounds. After working at the Institute of Inorganic Chemistry at the University of Innsbruck, he joined the Medical University in 1975, where he is retired Associate Professor for Technical Hygiene. In 1991, he succeeded in synthesizing the endogenous oxidant N-chlorotaurine in crystalline form. His main interests comprise development of new halogen-based active agents and exploration of the chemism of bactericidal processes.

Dmitri Debabov is a microbiologist with drug discovery and development experience. After completing his Ph.D. in 1994, Dmitri continued his training as a postdoctoral candidate at Northwestern University in Chicago to study cell wall biosynthesis of Gram-positive bacteria. In 2000 to 2006, Dmitri worked at Theravance, Inc., where he participated in the discovery and development of telavancin (Vibativ), a novel glycopeptide antibiotic against Gram-positive pathogens that is currently on the market for use in the treatment of complicated skin and skin structure infections (cSSSI) and pneumonia. Since 2007, Dmitri has worked at NovaBay Pharmaceuticals, Inc., where he is currently Director of Microbiology and Cell Biology. Dmitri works on discovery and development of active chlorine compounds as topical antimicrobials. His research interests include antibacterial, antifungal, and antiviral activity, mechanism of action, potential for resistance, and activity against biofilms in studies of novel dimethylated N-chlorotaurine analogs.

Continued next page

Markus Nagl is an M.D. and a specialist in hygiene and microbiology and general medicine. After his postdoctoral education at the University of Innsbruck, he was employed at the University College London (The Rayne Institute) in 2000 and 2001, working on oxidants produced by neutrophilic granulocytes. He has been Associate Professor for Hygiene and Microbiology at the Innsbruck Medical University since 2003 and works mainly on the development of active chlorine compounds as topical anti-infectives. This work includes both preclinical studies on the activity and mechanisms of these antimicrobial agents in innate immunity and clinical trials on their tolerability and efficacy to cure infectious diseases. Accordingly, Markus obtained a diploma for clinical studies in 1998, and he has been a Qualified Person for pharmaceutical quality management since 2012. Beside the original endogenous substance N-chlorotaurine, its novel dimethylated analogs became topics of main interest.