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A REVIEW ON MOLECULAR IODINE (I_2) AND ITS TOPICAL APPLICATION ON SKIN AS AN ANTISEPTIC

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ABSTRACT

Molecular iodine(I_2) has been used as one of the most effective antimicrobial agents as antiseptic as well as disinfectant. It has in use for many years as an antimicrobial agent in hospitals, laboratories and in the world of pharmaceutical industry. Molecular iodine(I_2) in its different chemical form has a number of beneficial effects on human being internally and externally but in this review paper we have mentioned the use of molecular iodine(I_2) as an antimicrobial agent when applied topically to the human skin. Many published literatures and research papers show that molecular iodine among the different chemical forms of iodine is acting as antiseptic and disinfectant, responsible for the antimicrobial effect and also concluded by many studies that molecular iodine(I_2) has broad spectrum antimicrobial activity on almost all species of microbes such as bacteria, fungi, algae, virus etc. Molecular iodine(I_2) has been proved for its non-irritant and non-harmful behaviour when applied as topical agent on skin and has been in use for almost 200 years as topical antiseptic for application on cuts, wounds, skin etc. The purpose of this review paper is to assemble and gather the fragmented data or information about the

molecular iodine, its uses, antimicrobial properties, topical application on skin with the help of various studies and research that had conducted in the past and prove that molecular iodine(I_2) is one of the ideal antimicrobial agents among the all-existing antimicrobial agents.

KEYWORDS: Molecular iodine (I_2), topical antiseptic, antimicrobial, disinfectant, microcidal agent.

INTRODUCTION

Topical antiseptic agents popularly used for skin antisepsis and disinfection, must have a broad-spectrum activity, fast prolonged action, easy diffusion through the skin surface with minimal toxicity and very low or no irritation against normal skin flora. According to WHO and CDC guidelines there are many agents approved and recognised by healthcare authority that provide antiseptic effects, among them molecular iodine(I_2) has proved to be an ideal agent as a skin antiseptic and disinfectant. Iodine has several chemical forms including elemental/molecular iodine(I_2), iodates, iodides, periodate etc. In all these forms, the form responsible for antimicrobial effect is free molecular iodine(I_2).[22] Molecular Iodine(I_2) was first discovered by M. Courtois a chemist of Paris in the year 1812.[14] Molecular iodine(I_2) exists in solid state and sublimes itself directly into gaseous phase.[19] Molecular iodine (I_2) is a homonuclear stable molecule provides different therapeutic effects at different concentration as well as has activity against all microbes with safe human topical administration. Molecular Iodine(I_2) has been in use for nearly 180 years as an antimicrobial agent because of its high reactivity against wide range of microbes.[22]

Molecular iodine(I_2) act as a broad-spectrum antimicrobial agent which prove to be a potent topical antiseptic agent known to its antipathogenic activity. One of the first antiseptic preparation of molecular iodine(I_2) was used in the care and healing of wounds and was proved to be very effective as its acceptance for providing antiseptic, wound healing and skin regeneration properties.[21][18] Weak solutions of molecular iodine(I_2) have been used as a powerful microbiocidal agent for the disinfection of unbroken skin before surgeries.[19] Also, it has been found to be beneficial topically in the treatment of various skin diseases like psoriasis, urticaria, dermatitis etc.

Molecular iodine(I_2) being the active form against all the microbes has already proved by many scientific research communities. In aqueous solutions iodine forms at least seven iodine species in a complex, among them molecular iodine(I_2) has proved to be responsible for

antimicrobial efficacy.[7] From many studies done on iodine species and its evaluation for germicidal effect, it is concluded that free molecular iodine(I_2) is almost entirely responsible for the actual microbiological activity in the preparation.[32] Another quantitative study of related sporicidal and bactericidal activity of diatomic iodine(I_2) and triiodide carried out by Wyss and Carroll showed that the triiodide(I_3^-) ion had negligible activity as compared to molecular iodine(I_2) against microbes during their testing on organism i.e., Bacillus Metiens spores, micrococcus pyogenes var. aureus and E. Coli.[40][7]

In a study "Enhanced topical delivery of non-complexed molecular iodine for methicillin staphylococcus aureus decolonisation" it has been concluded that formulation of molecular iodine (I_2) combined with safe organic emollient glycerine delivers high local concentration of the active antimicrobial entity I_2 with minimal evaporative loss, exhibit activity at 1ppm against MSRA (Methicillin – resistant staphylococcus aureus) and another important gram positive and negative human pathogen.[39]

BROAD SPECTRUM ACTIVITY OF MOLECULAR IODINE

Molecular Iodine(I_2) has proved for its broad spectrum of activity, speed of kill and lack of tendency to induce resistance which resulted in its acceptance as an active agent in topical disinfectants and sterilization.[15][9][17] Microcidal activity of an antiseptic is an advantage over micro static activity in the ideal characteristics of antimicrobial agent. Molecular iodine(I_2) has recommended as a microcidal agent responsible for microcidal efficacy in different formulations of iodine and has many important beneficial effects on humans in preventive care.[21]

As per data it is found that active agent Molecular Iodine(I_2) is rapidly bactericidal[38], fungicidal, tuberculocidal, virucidal and sporicidal in nature.[10] Antifungal activity of molecular iodine(I_2) has been proved against various fungi which cause diseases in human being like aspergillosis, taenia pedis etc. It also acted as efficient algaecides (dark blue green algae).[6] A research study conducted by Ostrec concluded that molecular iodine(I_2) has great impact on yeast (saccharomyces cerevisiae) causing inhibition of its growth, accumulation and metabolism.[30] Recently during the pandemic situation of COVID - 19 Molecular iodine (I_2) has been evaluated for its antiviral effect and has proved to be effective against SARS-COV-2 virus with its activity starts in 15 seconds.[29] It was also found in a case study that molecular iodine(I_2) as an external application got great advantage in the treatment due to its

broad-spectrum property in skin diseases like psoriasis inverterata, dermatitis[14] (Refer the table below).

Table 1: Broad Spectrum Activity Of Molecular Iodine(I_2) Against Various Microbes.

MICROORGANISM	SPECIES	ACTIVITY
BACTERIA	(Bacillus Metiens, micrococcus pyogenes var., aureus, E. coli, Methicillin-resistant staphylococcus aureus)	Yes
YEAST	(Saccharomyces cerevisiae)	Yes
VIRUS	(Mumps, herpes simplex, rubella, measles, influenza, HIV, SARS-COV-2)	Yes
FUNGI	(Trichophyton rubum, pityriasis versicolor, M. Canis, aspergillus niger, articulli)	Yes
ALGAE	(Dark blue-green algae)	Yes

MECHANISM OF ACTION

Molecular iodine (I2) is a rapidly acting, broad-spectrum microbicidal agent, has been in use for more than a century, acts by iodinating and oxidizing microbial protoplasm.[38] Molecular Iodine(I_2) rapidly penetrates into microorganisms and attacks key groups of proteins in particular the free - sulphur amino acids cysteine and methionine nucleotides), and fatty acids[8] which culminates in cell death. The good penetrating qualities of molecular iodine (I_2) also enhances its activity against many resident bacteria.[11] Antiviral mechanism of action of molecular iodine(I_2) seems to be similar as in bacteria.[34]

Antifungal activity of molecular iodine(I_2) was described by many scientists in many books which state that molecular iodine(I_2) acted as an active agent against fungus Hematodes.[14] Also, in a case study of a physician where a case of white swelling (fungus articuli) treated with the help of molecular iodine(I_2) solution externally proves its action as an antifungal agent.[14]

PROPERTIES OF MOLECULAR IODINE(I_2)

WHO and CDC guidelines stated that molecular iodine(I_2) is nonstaining, odourless, free of toxicity and non-irritant in nature. It has been proved in many studies that molecular iodine(I_2) shows the ideal properties of an antiseptic agent when applied topically on the unbroken skin as well as on the broken skin with wounds, cuts and burn scars.[5] Molecular iodine(I_2) being an active antimicrobial agent used with various iodophors for its release in free form and of stability and solubility purpose according to CDC 2008 guidelines.

Staining and odour

Molecular iodine(I_2) satisfied the conditions of an ideal topical application as it does not leave any stain or colour as when it applied topically on skin as well does not leave any foul odour.[38] It has been documented in CDC guidelines of "IODOPHORES" that molecular iodine(I_2) is not responsible for staining and pungent odour as the formulations contain many solubilising agents and complexes in much greater amount as compared to molecular iodine and these other species cause staining and responsible for odour of the formulation after application.

As per study by Black et al in 1958 it has been revealed that using molecular iodine(I_2) as an antiseptic or disinfectant leaves no colour, no perceptible odour or taste, while other iodine formulations cause skin staining after application.[6] Like in the case of povidone iodine and Lugol's solution (strong iodine solution corresponding to USP XXI) produces a dark brown staining which cannot be removed by washing with soap and water or by moistening with reducing material and decreases very slowly observed even after 12h.[11] Another study also proved that saturated solution of molecular iodine (I_2) contains much more free molecular iodine(I_2) as compared to other forms and solution of iodine causes no stain on the skin or sometimes causes only slight colour which soon vanishes.[14]

Persistency

Molecular iodine(I_2) contains the beneficial persistency effect that implies the prolonged existence of its topical formulations which serves a great advantage in terms of therapeutic efficacy or action for a long time after removal of the application. As like as an ideal skin antiseptic molecular iodine exerts a persistent microbiocidal activity after application even after the removal of the preparation by washing away with water.[11] This 'persistent action' or 'residual effect' is usually due to alterations in the skin surface, back-diffusion that regarded as an advantage.[12] Pharmaceutical world has many formulations of molecular iodine with different iodophors such as povidone iodine, Lugol's iodine, iodides, molecular iodine in glycerine etc. In many studies it has been documented that molecular iodine(I_2) with emollient glycerine provides high antimicrobial effect with minimal evaporative loss and hence gives good persistency depends upon the concentration of free molecular iodine(I_2), contact time and the dimension of the treated area and the nature of the treated skin.[11][39]

Safety profile

Molecular iodine(I_2) is found to be non-irritating and non-toxic than other forms of iodine when applied externally.[14] Molecular iodine(I_2) is non irritating and nontoxic in nature (Tripathi; 2013). Because of its non-irritant and non-toxic behaviour, Molecular iodine (I_2) can be applied in many other areas such as in bandaged or occluded skin without risk of blistering, on boils, furunculosis, burns, otitis externa, ulcers, tinea etc due to its non-toxic nature.[38] Molecular iodine(I_2) is well tolerated on its topical application on unbroken skin and on wounds in long term uses.[3]

ANTISEPTIC USE IN WOUND CARE

Molecular iodine(I_2) has been described as the most potent antiseptic available for the application in wound care.[33] One of the first antiseptic formulation of molecular iodine(I_2) used for the treatment and disinfection of wounds and cuts was developed in 1829.[18] Molecular iodine(I_2) not only provide antiseptic effects on wound but also provide epithelialisation of chronic wounds.[25][28] Many studies in past proved that molecular iodine(I_2) reduces the inflammation, wound healing time[1] and not associated with the development of resistance against microbes[24], also it is effective in the treatment of acute and chronic wounds and heal them in less time as compared to other antiseptic formulations available in the market.[5] Molecular iodine(I_2) has also showed anti-inflammatory property as it is effective in the treatment of wounds in the burn patients and reduces the healing time of the burn scars with providing anti-inflammatory effect.[3]

ANTISEPTIC USE IN DERMATOLOGY

Molecular iodine(I_2) has been used as an active dermal agent in the treatment of inflammatory, immune-mediated and infectious diseases for a long time, moreover topical application of molecular iodine(I_2) has been reported to provide protection against sulphur-mustard-induced skin lesions, heat-induced and acid-induced skin scars.[13] Molecular iodine(I_2) a useful antiseptic agent in the dermatologic armamentarium. It is successfully used for inflammatory dermatoses, erythema nodosum, subacute nodular migratory panniculitis, nodular vasculitis, erythema multiforme, and Sweet's syndrome. Also, molecular iodine(I_2) is successfully used for cutaneous and lymphocutaneous sporotrichosis.[35] It has been proved by many scientific studies and literatures that molecular iodine(I_2) is the drug of choice for sporotrichosis[16] and also, many studies revealed that molecular iodine(I_2) when applied to the folliculitis condition, the hyphae were damaged rapidly, the lesion contracted gradually,

necrosis of tissue was broken off, and collagen fibres were repaired to scarring or returned to certain favourable outcomes of cured folliculitis.[26]

ANTISEPTIC USE IN ORAL HYGIENE

Molecular iodine(I_2) is the ideal antiseptic used in oral hygiene practice of keeping one's mouth clean and free from diseases and other problems. It has been proved in many studies that molecular iodine(I_2) as oral antiseptic rinse in vitro completely inactivates SARS-COV-2 virus, at its lowest concentration and at the lowest contact time.[4] Oral antiseptic formulations of molecular iodine(I_2) have proven to be a good alternative for the management of the mouth lesions in mouth caused by various categories of bacteria, as there is a very low risk of systemic toxicity or no allergies and bacterial resistance. Molecular iodine(I_2) has been proved to be the most effective antiseptic in oral wound repair, due to its antimicrobial, anti-inflammatory and antioxidant properties.[36] Topical application of molecular iodine(I_2) after cleaning and irrigation of the oral cavity inhibited bacterial growth in the oropharyngeal fluid of patients on mechanical ventilation and not disrupting the balance of the oral microbiota.[37] From many studies it is concluded that molecular iodine(I_2) has been proved to be an ideal antiseptic for oral care and hygiene with broad-spectrum anti-infective activity and low resistance potential in both infection control and prevention.[20]

CONCLUSION

From the review point of view (PubMed, science direct, Cochrane database etc), it is concluded that Molecular iodine (I_2) has proved as broad-spectrum antimicrobial agent as it is active against all groups of microorganisms such as gram positive and gram-negative bacteria, fungi, algae, viruses. It contains all the properties of an ideal antiseptic. Topical formulations of Molecular iodine(I_2) have been accepted and used for almost 200 years as antiseptic and disinfectant. It has also proved to be non-toxic in nature when applied topically on unbroken skin and contains few allergic reactions when administered internally. It is also found to be safe and effective antiseptic agent by various researches and reports on broken skin and wounds with no anaphylaxis reactions. From a number of studies, Molecular iodine(I_2) is concluded as an ideal topical antiseptic agent due to its broad-spectrum activity, non-staining, non-toxicity, odourless, wound healing and persistent property and exhibit a wide scope to be explored in many medical areas.

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