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Evaluation of Clinical efficacy and safety of Methyl sulfonyl methane and N-acetyl cysteine in Cancer chemotherapy and irradiation induced Oral mucositis.

Radhika Rani K C[1], N.Anitha[2]

[1]*Associate professor ,Department of Pharmacology, S.V.Medical college, Tirupati, Andhra pradesh, NTRUHS*
[2]*Assistant Professor,Department of Pharmacology, S.V.Medical college, Tirupati, Andhra pradesh, NTRUHS*

Abstract:
Background*: Treatment of cancer is increasingly effective, but associated with short and long term side effects, including oral mucositis or its associated pain in patients with cancer receiving chemotherapy or radiotherapy.* ***Objective****; To evaluate the clinical efficacy and safety of Methyl sulfonyl methane and N-acetyl cysteine in cancer chemotherapy and irradiation induced oral mucositis* ***Materials and Methods****; 30 Patients with oral mucositis received MSM 1000mg thrice daily and NAC 600mg twice daily for 7-10 days. Patient is evaluated by using validated WHO and RTOG scoring system of physicians and patients.* ***Results****; improvement in oral mucositis was not significant with MSM (P< O.O67) while improvement with NAC was highly significant (P<0.0001)* ***Conclusion****; NAC a safe drug significantly reduced chemotherapy and irradiation induced oral mucositis compared with MSM.*

Keywords: *Cancer chemotherapy , Oral mucositis , N-AcetylCysteine, Methyl sulfonyl methane*

I. Introduction

Annually there are approximately 4,00,000 cases of drug treatment induced damage to the oral cavity(1). The oral complications which arise as a result of cancer therapy particularly chemotherapy and localized radiation therapy include mucositis, xerostomia (drymouth), bacterial, fungal or viral infection, dental caries, loss of taste, trismus and osteoradio necrosis(2). Oral mucositis is the most frequent and potentially severe complications of cancer therapy.(3,4), which may manifest as erythema, desquamation, ulcer formation, bleeding and exudates. The probability of developing mucositis is dependent upon the treatment modality. Approximately 40% of patients treated with standard chemotherapy develop mucositis compared to 76% of patients who receive high dose chemotherapy and undergo bone marrow transplantation. Between 30% and 60% of patients receiving therapy for cancer of the head and neck develop mucositis, and greater than 90% of patients receiving concomitant chemotherapy and localized radiation therapy are affected.(1,5)

Patients with mucositis can have many symptoms. Mucositis usually begin with swelling, redness and erythema of the mucosal membranes followed by the development of white elevated desquamative areas that progress into painful pseudomembranous lesions.(5) Patients may complain of pain, dry mouth, burning and tingling of the lips. The pain associated with mucositis is often intense and can be exacerbated by attempts to eat, drink, swallow or speak. The pain may be so severe that it limits adequate nutritional and liquid intake, thus putting patients at increased risk for dehydration and malnutrition. Proper assessment of oral mucosa is of paramount importance, before initiating chemotherapy and throughout a treatment course. A variety of grading systems have been established.

N – ACETYL CYSTEINE : It is a synthetic derivative of the naturally occurring amino acid L-cysteine. It reduces the viscosity of mucus and other secretions. It is thought to act by reducing disulphide bonds in protein and altering their configuration to improve flow characteristics. It is readily converted to cysteine and by stimulating hepatic glutathione synthesis. It effectively prevents acute paracetamol – induced hepatotoxicity.

As a nucleophile, it can protect against effects of ionizing radiation, and the toxicity of agents such as alkylating cytotoxic drugs and some halogenated hydrocarbons. N- Acetyl cysteine potentiates the vasodilator actions of nitroglycerin and can reverse tolerance to nitrates.

Acute, subacute and chronic oral and parentral toxicity studies in mice, rats, rabbits, guinea pigs and dogs, including test for mutagenicity, teratogenicity and effects on fertility, did not demonstrate any results of potential clinical significance[11]. Oral N- Acetyl cysteine reduces sputum viscosity and facilitates expectoration in patients with bronchopulmonary disease with improvement in symptoms and lung function tests.

N-Acetyl cysteine protects against the acrolein – induced hemorrhagic cystitis caused by cyclophosphamide and isophosphamide without reducing anti-tumour activity[12]. Skin reactions to radiation therapy may be reduced by topical N-Acetyl cysteine[9].

The antioxidant N- Acetyl cysteine is a precursor of intracellular glutathione (GSH). Glutathione is a ubiquitous intracellular thiol present in all tissues including lung, besides maintaining cellular integrity by creating a reduced environment, GSH has multiple functions, including detoxification of xenobiotics, synthesis of proteins, nucleic acids and leukoteriens. It protects lungs from oxidative injury.

Cysteine and glutathione actively participate in catabolic conditions and immunological dysfunction. Treatment with N-Acetyl cysteine , a thiol containing antioxidant was found to increase the plasma albumin level and to ameliorate the loss of body cell mass in cancer patients and healthy individuals. N – Acetyl – L – cysteine exhibits antitumur activity by increasing tumour necrosis factor alpha – dependant T- cell cytotoxicity without showing any toxicity.

Oral administration of NAC reduces the angiogenic response induced by kaposis sarcoma tumor cell products , conforming the ability of N- Acetyl Cysteine to inhibit the invasive activity of endothelial cells invivo and there by blocking angiogenesis[15]. The antimutagenic and anticarcinogenic properties of NAC could be ascribed to multiple protective mechanisms, such as NAC nucleophilicity, antioxidant activity, its ability to act as a precursor of intracellular reduced GSH, modulation of detoxification, and DNA repair processes. On these grounds NAC has emerged as a most promising cancer chemopreventive agent[15]

N- Acetyl cysteine affects the process of tumor- cell invasion and metastasis, probably due to inhibition of gelatinases by its sulfhydryl group, with the possible contribution of other mechanisms, including the potent antioxidant activity of this thiol. It has the potential to impact upon tobacco smoke carcinogenicity in humans because it can modulate certain cancer – associated biomarkers in specific organs[9]

Pharmacokinetics:

N-Acetyl cysteine may be assayed in plasma and urine by gas liquid and high performance liquid chromatography with detection limits of 50μg 1^{-1}. Following an oral dose a mean maximum plasma concentration was achieved in 1hour. The drug disappears rapidly from plasma with a half life of 0.5 to 6.6hrs. N-Acetyl cysteine is extensively bound to plasma (78%) and to tissue proteins by labile disulphide bonds and rapidly deacetylated to cysteine and oxidized to disulphides.

N-Acetyl cysteine is available in oral, topical, inhalation and intravenous formulations. In adults dose of 200mg three times daily can be given. It can be given in

- Respiratory disease: It is administrated by nebulisation or orally for it's mucolytic action.
- Keratoconjuntivities: For symptomatic relief of "dry eye" 1 or 2 drops of the 5% solution are instilled into the eye 3 – 4 times daily.
- Paracetamol poisoning: N-Acetyl cysteine protects against paracetamol induced hepatotoxicity by facilitating glutathione synthesis in the liver.

Adverse reactions:

Accidental over dosage of intravenous N- Acetyl cysteine causes manifestations that include rash, flushing , nausea and vomiting , bronchospasm , oedema , tachycardia and hypotension. It has the ability to modulate a variety of DNA damage and cancer – related- endpoints. it inhibits cell progression in pancreatic carcinoma cells.

Methyl Sulfonyl Methane (Msm) :

Methyl sulfonyl methane (MSM) is a naturally occurring biosulfur and dietary derivative of Dimethyl sulfoxide (DMSO). It is present in food and in human body and animal tissue and also in plants. It consists of two hydrocarbon units attached to a unit with one sulfur and two oxygen atoms.

MSM is made from DMSO. DMSO is a well known therapeutic agent derived from trees. DMSO is widely used around the world for relief of arthritis, muscle and skeletal disorders, acute head and spinal cord trauma, athletic injuries and other conditions. In the US ,it is approved by the FDA for the treatment of interstitial cystitis, a painful inflammatory disorder of the bladder.MSM delivers many of the remarkable healing properties of DMSO -but without the annoying odour of DMSO.MSM is a source of sulfur, a mineral critical to the normal function and structure of the body.

Sulfur is a raw material for the protein and connective tissue that make up our body mass, for enzymes that conduct chemical reactions, and for powerful natural compounds that protect us against toxicity and harmful oxidative stress[16].

Sulfur is a major ingredient of important amino acids – the building blocks of proteins. Proteins are the primary constituent of enzymes, hormones, antibodies and the biochemical activities going on in the body.

Methyl sulfonyl methane

- It is an analgesic, it relieves pain
- It reduces inflammation
- It passes through cellular membranes of the body including the skin

- It dilates blood vessels (vasodilatation) and increases blood flow.
- It is a cholinesterase inhibitor. Cholinesterase is an enzyme that stops excessive passage of nerve impulses from one nerve cell to another. It provides relief of constipation associated with ageing. it helps to restore normal bowel activity (peristalsis).
- It reduces muscle spasm and provides muscle relaxation.
- It alters the cross linking process in collagen thus reducing scar tissue.
- it has antiparasitic properties particularly for giardia, a protozoan parasite that causes diarrheoa.
- It has an immune normalizing effect.

MSM is a safe drug. In long term toxicity trails we found no toxic effects with oral dose of 8grams per kilogram (2.2 pounds)of body weight. For MSM, the LD-50, was more than 20gm for each kilogram of the weight. MSM is the least toxic substance in medicine.

MSM relieves pain through the following actions

- The inhibition of pain impulses along nerve fibers.
- Lessening of inflammation.
- Increase of blood supply.
- Reduction of muscle spasm
- Softening of scar tissue

MSM helps to relieve inflammatory conditions such as crohn's disease and ulcerative colitis[17]. It also helps to reduce the inflammation in the joints

a. Ii Materials And Methods

This study has been supported by Clinical Pharmacology, Nijam's institute of Medical Sciences, Hyderabad In the present comparative study, outpatient and inpatients from the Departments of Medical Oncology and Radiation Oncology were recruited as trial subjects. All subjects were clinically examined and evaluated for fulfillment of inclusion and exclusion criteria and eligibility for study enrolment was confirmed.

In our earlier pilot study, in twenty patients of mucositis, MSM was compared for its efficacy and safety versus placebo. It was observed that, though administration of MSM 1000 mg thrice daily for 7-10 days, did show slight improvement in mucositis, the overall effect was however not statistically significant. Thus in the present study, thirty patients with mucositis initially received MSM 1000 mg thrice daily (initiation phase) for 7 to 10 days. Subsequently all patients who continued to have mucositis with WHO score of $\geq$ 1 at the end of MSM therapy, received NAC 600 mg twice daily (continuation phase) for further period of 7-10 days.

II. Iii Results

The degree of severity of mucositis was evaluated by well-validated scoring system (WHO & RTOG grading of Mucositis by physicians and patients) as detailed given in the methodology. Well-defined scoring system ranging from 0-3 was used to grade the mucosits.

The mucositis score grading by physician (WHO Criteria) was shown in Table-1. Before the administration of test drug the mean score was 1.867 ± 0.776 with 95% confidence Interval (1.57 - 2.15). Administration of MSM and NAC significantly reduced the mucositis score. (ANOVA). P-Value <0.0001) Improvement in mucositis was not significant with MSM (P-<.067) while the improvement was highly significant with NAC P-<0.0001 (Wilcoxons matched pair test). In WHO physician mucositis score, NAC was found to have more significant improvement in mucositis as compared to MSM (P<0.0001) The mean change in the scoring as well as percentage decrease in the WHO physician grading, with MSM & NAC as compared to base line is shown in (Fig-1 and Fig-2) NAC was found to be significantly effective in lowering the mucositis than MSM. The decrease in mucositis was 12% with MSM while it was 48% with NAC (P<0.0001).

Similarly to physician WHO grading degree of mucositis grading given by patients also showed significant improvement both with MSM & NAC. The mean score of patients grading with Analysis of variance (ANOVA) is shown in Table-2. The mean score of 2.33 ± 0.88 at base line reduced to 2.06 ± 0.944, and 1.46 ± 1.0 with MSM & NAC respectively. Both the treatment produced statistically significant change in mucositis P<0.0002. In further analysis (wilcoxins matched pair test) it was found that NAC produced significant reduction of score than MSM (P<0.001)`` As compared to physician's score there was a statistically significant improvement in patients score grade with MSM as shown in Fig-1.

III. Discussion

In our study with 7 to 10 days treatment, we observed good reduction in mucositis in cancer patients. The improvement in mucositis scores both by physicians and patient was found to be comparatively more significant with NAC then MSM. The percentage reduction in overall mucositis symptoms was much more with NAC. In a study topical application was tested for its ability to attenuate the course of radiation induced

oral mucositis in established hamster model. In this model topical application of NAC demonstrated good effect.[18] The antioxidant NAC is a precursor of intra cellular glutathione (GSH) and is also well known as one of the chemopreventive agents which acts through a variety of cellular mechanisms.[(14)] In one study topical application of Vitamin E was shown to reduce the oral mucositis and promote the ulcer healing in paitints receiving chemotherapy. Vitamin E prevents the peroxidation of membrane polyunsaturated fatty acids and membrane stabilizing effects which is attributed to anti oxidant activity[19]. NAC is a potent antioxidant. This activity hasbeen confirmed in the treatment of apthous ulcer[20].NAC is a precursor of intracellular cysteine and Glutathione. NAC has an impressive array of mechanisms and protective effects towards DNA damage. In Chemotherapy and radiation induced mucositis there is marked increase in oxidative stress. Antioxidants have been shown to reduce the mucositis. In present study our patients were receiving different combinations of chemotherapeutic agents with or without radiation. We did not analyze, any preferential effect against particular chemotherapeutical agent. Overall effectiveness was found to be significantly much better with NAC than MSM. This difference in the effect is probably because of potent antioxidant activity of NAC, which is either absent or low in MSM.

IV. Conclusion

Chemotherapy and radiation induced oral complications and mucositis in particular are significantly associated with oxidative damage. We observed that N-Acetyl cysteine significantly reduced mucositis. Methyl sulfonyl methane also found to be effective in relieving pain in mucositis. NAC which is safe even in high doses and does not interfere with anticancer regimens can be used for management of mucositis.

Table-1 Who Physicians Mucositis Score Grading

variable	Basal	Post MSM	Post NAC
(N)	(30)	(30)	(30)
MEAN	1.867	1.633	0.9667
S.D	0.7761	0.7649	0.8503
S.E.M	0.1417	0.1396	0.1552
LOWER95% C.I	1.577	1.348	0.6492
UPPER 95% C.I	2.156	1.919	1.2884

Fig:1

TABLE NO. 2

Anova table	S.S	Df	MS
TREATMENT between groups	13.09	2	6.544
RESIDUAL within groups	55.4	87	0.6368

TABLE NO.3

wilcoxsons table	BASAL v/s MSM	BASAL v/s NAC	MSM v/s NAC
Sum of positive, negative ranks	54.00, -12.00	290,-16.00	190.0, -0.0000
Sum of signed ranks	42	244	190
P-value	<0.0674	<0.0001	<0.0001

TABLE NO.4 WHO PATIENTS MUCOSITIS SCORE GRADING

variable	Basal	Post MSM	Post NAC
(N)	(30)	(30)	(30)
MEAN	2.333	2.067	1.467
S.D	08841	0.9444	1.008
S.E.M	0.1614	0.1724	0.184
LOWER95% C.I	2.003	1.714	1.09
UPPER 95% C.I	2.663	2.419	1.843

Fig:2

TABLE NO.5

Anova table	S.S	df	MS
TREATMENT between groups	11.82	2	5.911
RESIDUAL within groups	78	87	0.8966

TABLE NO.6

wilcoxsons table	BASAL v/s MSM	BASAL v/s NAC	MSM v/s NAC
Sum of positive, negative ranks	**65.00,-13.00**	**302.0, -23.00**	**180.5, -95.00**
Sum of signed ranks	**52**	**279**	**171**
P-value	**<0.0425**	**<0.0001**	**<0.0001**

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