A CASE REPORT ON N-ACETYLCYSTEINE (MUCINAC) INDUCED CHEST TIGHTNESS

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ABSTRACT:
N-Acetylcysteine is anapproved drug by the Food and Drug Administration (FDA) and recognized by the World Health Organization (WHO) as an essential drug[1]. It isa synthetic N-acetyl derivative and prodrug of the endogenous amino acid L-cysteine, a precursor of the antioxidant glutathione (GSH), with mucolytic, antioxidant, and anti-inflammatory activities[4]. Primarily approved for the treatment of potentially hepatotoxic doses of acetaminophen. It is also used in the treatment of respiratory disorders, especially in COPD and cystic fibrosis[6].
An unusual case of chest tightness due to mucinac (N-Acetylcysteine) was reported in a female patientwith a history of cancer in the left upper alveoluswas admitted to the hospital for radiotherapy + chemotherapy. She was prescribed tablet mucinac for excessive mucus and to improve respiratory symptoms. The patient developed chest tightness after ingestion of mucinactablets.According to the Naranjo scale the observed reaction was a probable ADR.Later tablet was stopped, replaced nebulization with budecort respule.

Keywords: N-acetylcysteine, glutathione, antioxidant, anti-inflammatory, mucolytic, COPD, Cystic fibrosis, Chest tightness,

INTRODUCTION:

N-acetyl cysteine (NAC) is a prescribing drug which is a small single peptide molecule derived from amino acid L-cysteine that contains sulfhydryl group. The drug approved by the Food and Drug Administration (FDA) and recognized by the World Health Organization (WHO) as an essential drug[1, 2]. It is originally patented in 1960, and its use in medicine was first reported in 1967. Clinically it has been used in cystic fibrosis since 1969[3].

NAC is a precursor to glutathione (GSH)[4]. Glutathione is a potent antioxidant with many crucial functions including detoxification and CTL (cytotoxic T lymphocytes) activation. Most glutathione in the body is produced intracellularly in the liver from the amino acids. It is atripeptide composed with glycine, cysteine and glutamic acid[5]. The properties of NAC include enhancing glutathione S-transferase activity, repleting glutathione, scavenging free radicals, and stabilizing protein structures by crosslinking cysteine disulfide molecules along with its antioxidant action [3].

NAC acts as an acetylated cysteine residue to the amino acid L-cysteine; it can reduce various radicals, by donating one electron, or acts as a nucleophile by donating one or two electrons. Its chemical structure, formed by the sulfhydryl functional group and acetyl group linked to the amino group, is responsible for its metabolic activities related to the direct and indirect antioxidant action and mucolytic action[1].

The antioxidant action is directly linked to its ability to increase the levels of intracellular cysteine with subsequent increase in GSH. The isolated uses of both GSH and cysteine were not effective in raising GSH levels within cells, making NAC one of the major strategies to reduce the damage caused by oxidative stress in cases of xenobiotic intoxication, such as paracetamol or in pathologies related to GSH deficiency, through the maintenance of their levels in different tissues[1].Thus it is approved for the treatment of potentially hepatotoxic doses of acetaminophen (APAP), and it is almost 100% effective if given within 8 hours post-ingestion[6].

In addition, NAC is also able to break down thiol proteins (such as cysteinylated extracellular proteins) releasing free thiols with higher antioxidant capacity, which potentiates GSH biosynthesis. Another mechanism linked to the indirect antioxidant activity exerted by NAC is related to its reducing capacity. NAC is capable of restoring systemic pools of low-molecular-weight (LMW) thiols and reduced protein sulfhydryl groups, which are involved in the regulation of the redox state, as is the case with mercaptoalbumin, which is the main antioxidant present in plasma and extracellular fluids[1].

NAC also carries out one of its crucial activities as a potent expectorant. NAC is known as a mucolytic agent because it is able to reduce the disulfide bonds in cross-linked mucous proteins, interrupting their binding to the ligand and modifying their structures, thereby reducing the viscosity and elasticity of the mucus[1]. Thus it is used in the conditions with abnormal, viscid mucous secretions such as pneumonia, bronchitis, trachea bronchitis, cystic fibrosis, tracheostomy patients, postoperative pulmonary complications, post traumatic chest conditions and before diagnostic bronchoscopy to help with mucous plugging[6].

NAC also exerts anti-inflammatory activity by inhibiting the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which plays a critical role in the inflammatory

cascade and immune response involved in the response to oxidative stress. NAC blocks the translocation and nuclear activation of the transcription factor NF-κB, responsible for the regulation of pro-inflammatory gene expression. NAC has been shown to suppress the release of inflammatory cytokines TNFα, interleukin (IL)-1β, and IL-6 in lipopolysaccharide-activated macrophages[1].

Its off-label indications include acute hepatic failure, prevention of contrast-induced nephropathy, PCOD, neurological disorder, premature birth and recurrent pregnancy loss, and topical treatment of keratoconjunctivitis sicca[6].

In COPD, cystic fibrosis, and other lung conditions, nebulized NAC has mucolytic, anti-inflammatory, and antioxidant properties[6]. Oral NAC has also been tested as a medication that may influence oxidative stress and inflammation in COPD and thus led to an improvement in lung function and a reduction in the exacerbation and hospitalization rates[7].

CASE REPORT:

A 53 years old female patient with a medical history of cancer in the left upper alveolus, underwent inferior partial maxillectomy + MRND (modified radical neck dissection) at an outside hospital. Postoperative histopathological examination reveals, moderately differentiated squamous cell carcinoma, $PT_{4a}N_0M$ with a close margin. The patient was admitted to the department of radiotherapy for further treatment and planned for adjuvant specialized Radiation therapy- 3 DCRT (definitive chemo-radiation-therapy) up to 30 fractions in 6weeks and chemotherapy withweekly CISPLATIN (40mg) in our hospital. Past medical history reveals that the patient was a known case of hypertension, diabetes, and having chronic bronchitis for which she is on medication (Tab. Telmisartan 40mg, Tab. Pioglitazone+ Glimepiride, Tab. Levofloxacin) respectively. After the first cycle of radiation therapy patient was prescribed multiple drugsfor pain-relieving along with antihypertensive, oral hypoglycemic agents, and mucolytic drugs. During therapy,the patient developed chest tightness, nausea, and vomiting of one episode. The chest tightness was considered an adverse event and mucinac was the suspected drug to cause it. Even the concomitant drugs were evaluated for the cause of chest tightness and found nil. Hence mucinac has been withdrawn and switched to nebulization with budecort respule, injection ondansetron, and pantoprazole immediately and found the events subsides this shows dechallenge positive and final causality assessment was done.

Causality assessment of adverse drug reaction by using Naranjo scale from (table-1) [8]

Table -1: Naranjo Scale

QUESTIONS	**YES**	**NO**	**UNKNOWN**	**CASE ANALYSIS**
Are there previous conclusive reports on this reaction?	+1			+1
Did the adverse events appear after the suspected medicine was administered?	+2			+2
Did the adverse reaction improve when the drug was continued or a specific antagonist	+1			+1

was administered?				
Did the adverse reaction appear when the drug was re-administered?			0	0
Are there alternative causes that could have caused this reaction?		+2		+2
Did the reaction reappear when a placebo was given?			0	0
Was the drug detected in any body fluid in toxic concentrations?			0	8
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1			+1
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?		0		0
. Was the adverse event confirmed by any objective evidence?	+1			+1
SCORE				**8**

From the above Naranjo scale assessment the score reveals that it's a probable ADR due the drug N-Acetylcystein.

DISCUSSION:

Cancer patients often receive multiple drugs to maximize their therapeutic benefit, treat co-morbidities and counter the adverse effects of chemotherapy. Concomitant administration of multiple drugs increases the risk of drug interactions leading to compromised therapeutic efficacy or safety of the therapy[9]. The use of polypharmacy is prevalent among cancer patients. The presence of polypharmacy in cancer patients demands the screening of prescribed medications for timely prediction and prevention or minimization of any unwanted negative consequences as polypharmacy is inevitable among cancer patients[10].

Mucinac (N-Acetylcysteine) is a mucolytic and antioxidant drug. It is used in current medical practice in conjunction with chest physiotherapy as mucolytic in patients who have viscid or thickened airway mucus[11]. It has been reported to reduce the viscosity of sputum in both cystic fibrosis and COPD by facilitating the removal of pulmonary secretions. Moreover, maintaining the airway clearance prevents bacterial stimulation of mucin production and hence mucous hypersecretion[12].

Acetylcysteine can irritate the airways and induce bronchospasm when given by inhalation; therefore, it should be administered simultaneously with or following administration of an inhaled beta-adrenergic bronchodilator[11].

Its remarkable antioxidant and anti-inflammatory capacity is the biochemical basis used to treat several diseases related to oxidative stress and inflammation. The primary role of NAC

as an antioxidant stems from its ability to increase the intracellular concentration of glutathione (GSH), which is the most crucial biothiol responsible for cellular redox imbalance[1].

In European countries, NAC used as an anti-inflammatory drug as well as an antioxidant and it is believed to decrease the frequency of symptoms in patients with chronic bronchitis. In recent time, a comprehensive review in literature survey conducted and concluded in the field of the effectiveness of any oral mucolytic drugs that a decline of aggravations, days of disability and days of antibiotic treatment[13].

The adverse effects of NAC depend on the formulation and dosage used, which vary from mild to severe[6]. Through multi centric medical records an extensive reviews has shown that intravenous and oral NAC is associated with minimal side-effects[1].

In oral administration, the most common adverse effects are gastrointestinal symptoms such as nausea and vomiting, which occur in up to 23% of patients. Other reactions include itching and erythema [1]. The pungent smell of NAC, which resembles rotten eggs (due to sulfur), also contributes to manifestations of nausea and vomiting after oral administration[3]. NAC is commonly diluted in caffeine-free diet sodas to mask the smell and taste and to facilitate acceptance. Intravenous administration can also cause symptoms such as nausea and vomiting, with a frequency of up to 9%[1].

Adverse symptoms after administration of inhaled NAC include bacterial pneumonia, cough, sore throat, and drug-induced pneumonitis, among which coughing is the most common[1].

More serious adverse effects, such as anaphylactic reactions, are uncommon and more remarkable in up to 8.2% of patients. Anaphylactic reactions involve a response of non-immunological origin, probably related to the release of non-IgE-mediated histamine. They include cutaneous symptoms, such as flushing, itching, and angioedema, and systemic symptoms, such as bronchospasm and hypotension. The manifestations of cutaneous symptoms in anaphylactic reactions are usually greater, with a frequency of 75%[1].

N-acetylcysteine has anticoagulant and platelet inhibiting properties and the use in patients with bleeding disorders or blood thinners may be relatively contraindicated[3]. The use of NAC with patients on nitroglycerine should be cautioned, since it may cause hypotension[14]. Other more rare side effects may include stomatitis, drowsiness, rhinorrhea, and hemoptysis[3]. Recently a case report revealsthat severe chest pain developed due to N-acetylcysteine-induced esophagitis[15].

Chest tightness and bronchoconstriction have been reported with acetylcysteine. Clinically overt acetylcysteine-induced bronchospasm occurs rarely and unpredictably, even in patients with asthmatic bronchitis or bronchitis complicating bronchial asthma. Occasionally, patients receiving oral inhalation of acetylcysteine develop increased airway obstruction of varying and unpredictable severity. Patients who have had such reactions to previous therapy with acetylcysteine may not react during subsequent therapy with the drug, and patients who have had inhalation treatments with acetylcysteine without incident may react to subsequent therapy[16, 17].

N-Acetylcysteine was prescribed in this case for chronic bronchitis, which is a condition characterized with the presence of chronic productive cough for more than three months in each of two sequential years. Therefore, an important goal in the treatment of chronic

bronchitis is to decrease the frequency and duration of intensification, and to decrease symptoms in patients with aggravations.

In the current case, a cancer patient admitted for chemo with radiationtherapy. While assessing the medication history she was a hypertensive, diabetic, and having chronic bronchitis for that she is taking medication. At the time of chemo-radiation therapy she was prescribed with multiple drugs to improve the patient condition along with mucinac for wheezing. Later she developed chest tightness along with nausea and vomiting which is common during chemo-radiationtherapy. whereas chest tightness is the possible adverse effect caused by the NAC. However till know there is no literature evidences to this event.

The drug in the present case was immediately stopped and treated symptomatically by using nebulization with budecort respule andwith injection ondansetron, pantoprazole. Then the symptoms subsided and patient condition was improved after withdrawal of the NAC.

CONCLUSION

N-acetyl cysteine (NAC) is a well-tolerated mucolytic drug in the treatment of respiratory disorders especially in the case of COPD and chronic bronchitis, which moderates clinging mucous secretion and enhances glutathione S- transferase activity. Also it has been used widelyin paracetamol overdose.

In this case with the administration of N-Acetylcystin for chronic bronchitis, patient developed chest tightness. With the Naranjo scale assessment that the suspected reaction reveals that it’s a probable ADR.

The drug was withdrawn instantly and patient with chest tightness got relived by nebulization with budecort resuple. This is one of the immediate managements given for this condition. More care should be taken for further cases when NAC prescribed and also monitoring the patient regarding chest tightness. And caution is needed while using NAC in severe respiratory, cardiac and cardio pulmonary diseases.

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