Invest New Drugs (2012) 30:2080–2086
DOI 10.1007/s10637-012-9797-7

REVIEW

Potential mucolytic agents for mucinous ascites from pseudomyxoma peritonei

Krishna Pillai · Javed Akhter · Terence C. Chua · David L. Morris

Received: 13 December 2011 / Accepted: 20 January 2012 / Published online: 23 February 2012

Summary Pseudomyxoma peritonei is a disease characterised by the accumulation of mucinous ascites. Thus far, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to be effective at eradicating disease. Chemotherapy has been less effective, providing disease stabilization but not demonstrating significant treatment responses. Mucolytic is a potential class of drug that may be exploited in the chemical management of this disease. A variety of potential mucolytic agents are explored in this review providing evidence of basic biochemical evidence of its efficacy with potential translational application.

Keywords Pseudomyxoma peritonei · Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Appendix cancer · Mucolysis

Introduction

Pseudomyxoma peritonei (PMP) is rare clinical syndrome that is characterized by excessive mucinous ascites and mucinous peritoneal implants [1, 2]. The incidence of the disease is approximately two per 10,000 laparotomies with remarkable female dominance (female: male ratio being 3:1) [3, 4]. Appendiceal tumour is the main source of PMP [5] whilst other tumours such as fallopian tube, uterus, pancreas and stomach have also been reported [6, 7].

This disease is generally considered to be benign and bordering on malignancy, in some cases. It progresses with very few symptoms until excessive mucous accumulates in the abdomen leading to massive abdominal distension with consequential nutritional compromises [8, 9]. The long term survival of such patients remains poor, 5 year survival being 50% and 10 year survival in the region of 10–30% [10].

Current treatment involves laparotomy with cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) [11]. Subsequent accumulation of intra abdominal mucinous mass requires repeat laparotomy and this often leaves the patient with numerous compromises [12]. Hence, there has been a keen interest to formulate agents that may be used to disintegrate the mucin in situ and subsequent removal of the mass by a lesser invasive process such intra-abdominal lavage.

Biology of mucin

Mucin is a glycoprotein that is secreted by epithelial cells and other cells such as haematopoietic cells. It protects the cells from bacterial infection, harsh enzymic reaction and provides lubrication, particularly in ductal tracts such as respiratory, gastrointestinal and female reproductive system [13, 14]. Hence, it has obligatory functions in normal cells, however, in cancerous cells, there is an oversecretion of mucin which provides them with chemoresistance as well as invasive and metastatic properties [15, 16]. This over secretion of mucin may be due toxins, irritants and infection in normal cells [17]. In cancer cells, inflammatory cytokines [18, 19] are the main agents that initiate over secretion.

K. Pillai · J. Akhter · T. C. Chua · D. L. Morris
Department of Surgery Cancer Research Laboratories,
University of New South Wales,
Sydney, Australia

T. C. Chua · D. L. Morris (✉)
UNSW Department of Surgery, St George Hospital,
Hepatobiliary and Surgical Oncology Unit,
Sydney, Australia
e-mail: david.morris@unsw.edu.au

T. C. Chua · D. L. Morris
St George Clinical School, Faculty of Medicine,
University of New South Wales,
Sydney, Australia

The composition of mucin from respiratory and gastric origin has been well characterised [20–24], however, PMP mucin have been less frequently investigated. It has been suggested that MUC2 expressing goblet cells are mainly responsible for the secretion of voluminous mucin in PMP [25, 26]. Mucin is a glycoprotein whose monomers are linked together by glycosidic linkages. The polymeric mucin further has the propensity of forming cross linkages between each other through sulphur bond formation as shown below.

$$\mathbf{R-S-H + H-S-R \rightarrow R-S-S-R + 2H^{+} + 2e^{-}}$$

[R-S-H] glycoprotein with a sulphydryl group(-S-H)
[-S-S] disulphide bond

$$\mathbf{RS-SR + R'S-H \quad R'S-SR + RS-H (Thiol\ disulphide\ exchange)}$$

This property of forming intermolecular S-S bond between the mucin molecules as well as other protein molecules are often disrupted and reformed in such a way that there is a cross linking of the molecules (in a mesh like fashion). This is referred to as thiol disulphide exchange [27]. After numerous such reactions that are pH and enzyme dependant, an increasingly tangled mass of mucin develops. This process of cross linking gives mucin a more rigid structure. In PMP, some patients have very solid and gristly type of mucin. These type of mucins are a result of continuous inter crosslinking between mucin molecules and other materials such as cell debri (DNA, fibrin, lipids etc.) that accumulates in the peritoneal cavity over a period of time. Studies on the composition of hardened mucin from cystic fibrosis have shown the presence of a variety of components including DNA [28] and salt to be present in them. Further, one can also speculate that solidification may also result from loss of water that is probably expelled from the mucinous structure as a result of this cross linking process. Most solidified mucins on exposure to water, swell up and soften after a few hours indicating that the loss of water contributes to its hardening.

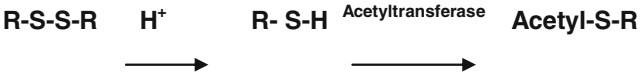
It has also been suggested that mucin may get hyperglycosylated and sulphated leading to mucin having high levels of fucose and sulphate [29, 30]. These processes may be aided by enzymes such as glycoslytransferase and sulphotransferase which works optimally at high pH (>7.0). Hence, these processes may increase the unit mass of mucin and contribute to mucin solidification process by providing additional areas for cross linking. Some other studies have shown that freshly secreted and post secreted mucin do not differ greatly in glycosylation and sulphation [31]. This may be due to variability of mucin secreted by cells in different regions of the body. It has also been postulated that the stickiness that is encountered in mucin is due to intermolecular bonds formed by calcium and magnesium ions that interact with negative charges on the tissue surface [32].

Application of mucolysis

Conceivably, softening (hydration) and mucolysis may be achieved by the reversal of processes that causes the solidification of mucin. Although the processes that may enable mucolysis of PMP mucin appear to be a straight forward task, lysis of glycosidic and disulphide bonds to soften and degrade mucin has met with limited success. This has been mainly due the composite nature of PMP mucin that does not undergo mucolysis with just a single mucolytic agent. Further, complexity of PMP mucin is due to its very heterogenous nature and hence any single agent or a combination of agents may not accomplish uniform mucolysis on all patient samples. However, on a theoretical basis, reversal of the various chemical processes that leads to solidification of mucin, as depicted in Fig. 1, may enable the dissolution of mucin.

Most commonly, agents that target the disulpide bonds (-S-S-) are used as mucolytics since it is believed that these cross linking disulphide bonds are mainly responsible for mucin solidification. Hence agents such as N-acetyl cysteine [33], mercaptoethanol [34], dithiotritiol (DDT) [35] are commonly employed as mucolytic agents. They act by breaking the disulphide bonds by reduction (addition of hydrogen). These reduced disulphide bonds are not stable and hence they may reform the disulphide bridge in such a way that there may be a reshuffling of the disulphide bonds [36].

Ideally, methods that reduce the S-S bond to S-H bond and then prevent the reformation of S-S bond will terminate the reaction. This may be achieved by acetylation [37] of the S-H group by enzymic reaction (acetyltransferases)



Although, this method of terminating the reformation of new s-s bond seems very attractive, in the biological systems, numerous biological reactions are dependant on acetylation [38] and hence, may interact with many endogenous biological molecules and reactions, thereby eliciting a host of undesirable reactions.

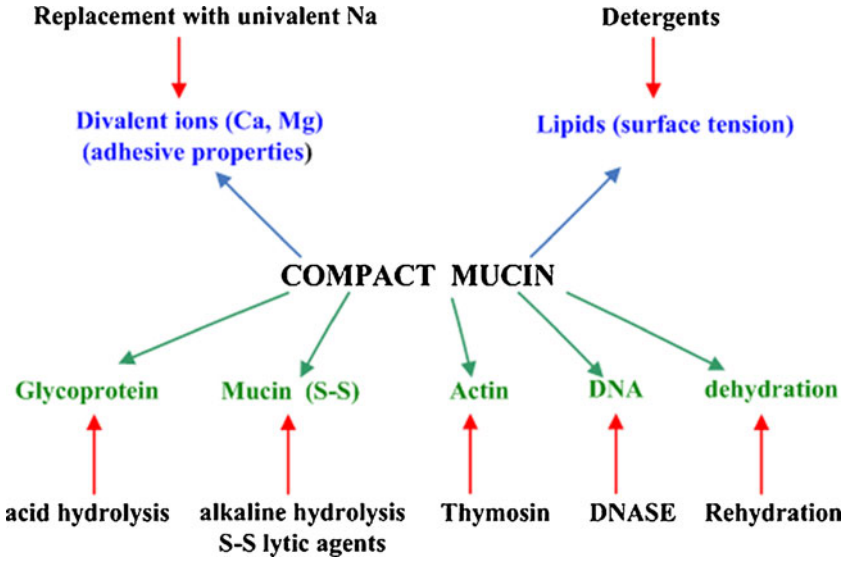


Fig. 1 Illustrates how factors that hold mucin together in a compact mass may be reversed by disruption of the cohesive elements with suitable chemicals

Potential mucolytic agents for dissolution of pseudomyxoma peritonei

Sodium bicarbonate

Sodium bicarbonate is an agent that is widely used in industrial application. It has buffering property. In solution it dissociates into sodium ion and bicarbonate ion, the latter can dissociate further into hydrogen and carbonate ions, as shown below:

$$NaHCO3 \rightarrow Na^{+} + HCO3^{-}$$
$$HCO3^{-} \rightarrow H^{+} + CO3^{-2}$$

[NaHCO3] Sodiumbicarbonate
[$HCO3^{-}$] bicarbonate ion
[H^{+}] hydrogen ion`
[$CO3^{-2}$] caronate ion

Hence depending on the requirements, sodium bicarbonate is able to produce an anion or cation to counteract the variation of pH. In a few reported cases, this agent has been used to disintegrate PMP mucins [39]. A strong solution of sodium bicarbonate (>5%) are very alkaline and the disruption of polymeric mucin is probably accomplished by alkaline hydrolysis [40] of the disulphide bonds. Adhesive properties of mucin due to presence of calcium and manganese ions may be reduced by replacement with univalent sodium ion [41]. A hypertonic solution of sodiumbicarbonate may also attract fluid and hence softening may also be contributed by hydration. Despite, the attractive chemical potential of this agent as a mucolytic, a recent case of alkalosis after irrigation with 7% solution of this agent [42] has been reported. Recently, we investigated the 7% sodium bicarbonate in an in vitro model of PMP mucin and found no mucolytic effect besides just hydration of the mucin (unpublished data).

Dextran and dextran sulphate

There have been several reports on the usage of dextran to soften PMP mucin and hence facilitate their removal by less

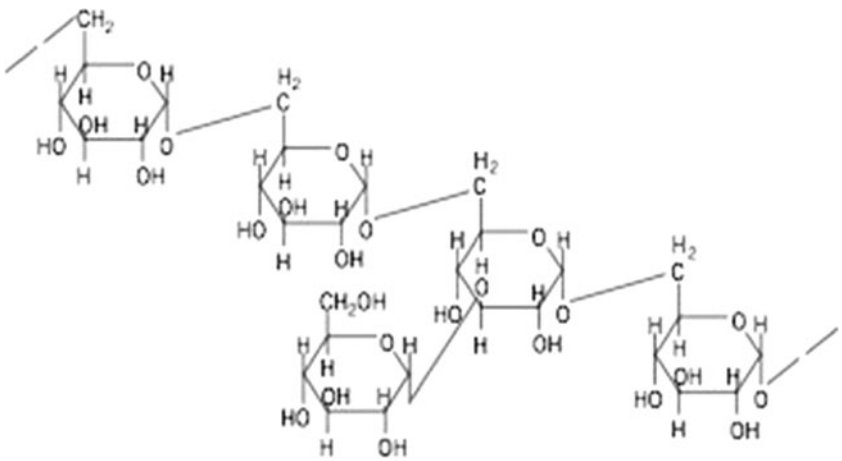


Fig. 2 Chemical formulation of Dextran

invasive processes. Dextrans (Fig. 2) are available in multiple molecular weights ranging from 10,000 Da to 150,000 Da. The larger dextrans are excreted poorly from the kidney and therefore remain in the blood for as long as weeks until they are metabolized.

Dextrans have been widely used by microsurgeons to decrease vascular thrombosis [43]. Further, owing to its large molecular size, it does not pass easily out of the vessels and hence act as potent osmotic agents (used for treatment of hypovolemia). A 5–10% dextrose solution have been used to disintegrate PMP mucin [44]. The mechanism by which this happens has not been fully investigated. It is most likely that a 5–10% dextran is able to attract large volumes of fluid and hence rehydrate the compact mucin. Hydration by itself is capable of disrupting some of the weaker intermolecular bonds [45]. We have investigated hydration of PMP mucin using phosphate buffer saline solution and we found that mucin from some patients may be softened by this process. Further, the thrombolytic mechanism of Dextran sulphate [46] may break down mucin and hence act jointly with hydration. Dextran sulphate on ionization may also disrupt the disulphide bonds, as well as the weaker hydrogen bonds. Hence, Dextran sulphate possesses mucolytic properties through more than one molecular mechanism.

Recent work by Shinohara et al. have reported that Dextran sulphate −12,000 MW, at 5% offers the best mucolytic effect compared to higher MW dextran sulphate or Dextran [47]. Others have shown that it causes hyperglycaemia, when given at 5–10% concentration [48, 49]. This may be expected, since dextran sulphate may be eventually converted into glucose. Further, negative mucolytic action of 5–10% dextran sulphate on PMP mucin has also been reported. This may largely be due to the great heterogeneity of the PMP mucin. Our investigation on dextran sulphate indicates that it has mucolytic properties, however, its action on PMP mucin seems to be very limited (unpublished data), as a single agent.

In our laboratory, we have worked on a variety of PMP mucin and our observation indicates that there are at least three or more kinds of mucin, the classification is based on hardness. The most compact form appears very gristly which can only be penetrated with a scalpel. Remarkably this gristly type of mucin softens after prolonged exposure (24 h) to mucolytic agents, however, they leave behind residues that are difficult to dissolve. These residues appear to be tissue like in nature and they are probably cell debris mixed with lipids.

Streptokinase and streptodornase

These two agents, derived from bacterial source, are currently used as thrombolytic agents. They are able to convert plasmin to plasminogen and hence reverse the process of fibrin formation [50]. There is only a single report where these two agents were used successfully in a female PMP patient [51]. Streptokinase 100,000 units, streptodornase 25,000 units in 20 ml of normal saline were injected at five widely separated abdominal sites and 24 h later with the help of an inserted large trocar and cannula, 4 pints of semi fluid blood stained mucinous material was removed. Recurrence of mucin accumulation was relieved by a similar process, 6 months later. The exact mechanisms by which mucolysis is achieved in PMP mucin by these antithrombotic agents have not been investigated, although it may be envisaged that through their anti fibrin activity they may be lysing fibrin type particles that has been shown to give some form of mucin its rigidity. More recent work has shown that dornase alpha is able to break up the size of DNA that are found in respiratory mucin and hence reduce the viscosity of mucin [52]. Additionally, if the mucin is heavily gorged with blood, the haemolytic effect of these agents may be very useful in liquefying this form of mucins.

N-acetyl cysteine

N-acetyl cysteine (NAC) is a sulphur containing amino acid that is a well known detoxifying agent for N-acetyl-amino cysteine overdose [53]. However, owing to its mucolytic properties, it is used liquefy mucus in respiratory diseases and in cystic fibrosis [54, 55]. Its main course of action is through its ability to reduce the number of disulphide bonds in glycoproteins and hence convert very viscous and purulent mucin to a state that allows ciliary clearance in the respiratory system [56]. It has also been found to be an effective mucolytic agent over a wide pH range (5.5–8.0) and allowing its use in humans without disturbing the pH balance of the body. However, owing to its low pKa (2.2), and hence reduced lipophilicity, its use as a topical agent is less effective. Although NAC has a long history as a mucolytic agent, it has not been used for PMP mucin. However our laboratory investigation indicates that it has mucolytic action on PMP, although its action is quite limited, as a single agent.

Hydrogen peroxide

Hydrogen peroxide is an oxidizing agent and its use as a mucolytic agent is less well known. Early experiments in 1940 [57] performed by a group showed that it acts as an oxidizing agent and converts the disulphide bonds in glycoproteins into sulphenic acid [58]. This property enabled the reduction of viscosity of gastric mucin recovered from rodents. Subsequent experiments revealed that the presence of ascorbic acid in hydrogen peroxide enhanced its oxidative and mucolytic property.

We have investigated the action of hydrogen peroxide (H2O2) and ascorbic acid (AA) as single agents, on PMP mucin and we found that that the mucolytic affect was strongly enhanced when these two agents were present together. The mixture (0.2% of AA/0.2% H2O2) performed optimally at 37 deg C. degrading PMP mucin over a period of 24 h. The downside of this mixture is that its performance was maximal at pH 4.0 and began to fall as the pH was increased. At pH 7.0, its mucolytic effect was diminished by at least 50% [59]. Hence, other agents may have to be added to enhance the mucolytic effect. N-acetyl cysteine may not be compatible with this mixture since the H2O2 may oxidize the molecule to an inactive state.

Other mucolytic agents

We have investigated the action of N-acteyl cysteine, Hydrogen peroxide, ascorbic acid and dextran as a single agent and in combination on a variety of mucin types. Our results (unpublished data) indicate that all these agents are able to perform mucolysis on PMP mucin; however their action seems to vary from patient to patient. Further, their activity as single agents is not sufficient to liquefy PMP mucin, hence, subsequent investigation with a combination of agents indicated that mucolysis was enhanced and that these combinatorial reactions may be used to disintegrate PMP mucin.

Conclusion and future directions

Mucolytics that have been commonly investigated are mainly for the disintegration of viscous mucin secreted in respiratory and gastric diseases such as chronic obstructive pulmonary disease, cystic fibrosis and other ailments related mainly to the respiratory system. The viscous mucin that is secreted during chronic obstructive pulmonary diseses has to be thinned down to a consistency to enhance ciliary propulsion. Similarly in cystic fibrosis, mucinous mass has to be reduced to a state for clearance. Unlike mucin from the respiratory or gastric system, PMP mucin accumulates in the abdominal cavity. The patient is relieved of this mucin mainly by laparotomy. A less invasive option is to disintegrate the mucin in situ and then remove it by intraperitoneal lavage. However, very little work has been carried out in this area, mainly due to rarity of the disease. The solubilization of intra-peritoneal mucin by introduction of suitable mucolytics and subsequent removal by catherization is a very attractive option since the process is less invasive and may be performed several times during the course of the disease without imparting severe injury to the abdomen. PMP patients require repeated removal of mucin, since after diagnosis and treatment, 50% of the patients live up to 5 years. At present, the disease is incurable and hence better clinical management of the disease is required.

Currently, the mucolytics that have been investigated on PMP suffer from two major disadvantages. Firstly, they do not perform uniformily on all patients and secondly they impart some systemic toxicity. The two agents that have been investigated are sodium bicarbonate and dextran sulphate. They have been successful only in some patients, although they carry inherent disadvantages such as alkalosis (sodium bicarbonate) and hyperglycemia (dextran, dextran sulphate). Streptokinase and streptodoronase have only been used in a women (single case report) with success, however there is no report of this agent being used recently.

Most of the mucolytic agents target the disulphide bonds and weaker bonds that can be broken by hydration. Very little work has been aimed on hydrolysis of glycosidic bonds, this may give an additive effect to the current agents (if reduction and hydrolysis can be achieved either together or individually using different agents). Further, there is a great patient variability in mucin composition and compactness; hence any single agent may not give a complete mucolytic solution on all PMP mucin. Therefore, more emphasis should be placed on using a combination of mucolytic agents to dissolve PMP mucin.

PMP patients generally succumb to the disease as a result of over secretion of mucus which sets up excessive intraperitoneal pressure that eventuates in nutritional compromises and finally starve the patient to death. Hence, currently, removal of mucin (cytoreductive surgery) and chemotherapy (hyperthermic intraperitoneal chemotherapy) are standard procedures for such patients. If treatment for PMP can be less invasive, then the quality of life of such patients may improve. Hence, there is a certain urgency to develop such agents that will facilitate the removal of PMP mucin easily in a less invasive manner.

Our laboratory is currently investigating a number of agents that will eventually be tested in animal models[60]. We are hopeful that both HIPEC and mucolysis can be carried out simultaneously through intraperitoneal lavage and hence short circuit the whole procedure with minimal patient recovery time.

Conflict of interest None declared.

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