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Oral Delivery of Antibodies

Future Pharmacokinetic Trends

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Summary

Antibodies have been investigated as specific targeting agents for cancer diagnosis and therapy, to inactivate toxic substances including drugs and also as passive immunotherapy for neoplastic or infectious diseases. In most cases the antibodies were administered systemically by the intravenous route. More recently, however, there has been increasing interest in the oral administration of antibodies for localised treatment of infections or other conditions in the gastrointestinal tract.

The normal physiological handling of ingested proteins is degradation by proteases in the stomach and intestine into small peptides or amino acids which are subsequently absorbed. Proteolytic enzymes involved in the degradation of orally administered immunoglobulins include pepsin, trypsin, chymotrypsin, carboxypeptidase and elastase. These enzymes initially degrade the antibodies to $F(ab')_2$, Fab and Fc fragments. The $F(ab')_2$ and Fab fragments, however, retain some of their neutralising activity locally in the gastrointestinal tract. Various approaches are possible to increase the stability of orally administered antibodies against proteolysis, including formulation in liposomes, coating with polymers and genetic engineering of resistant forms.

The clinical application of orally administered antibodies includes the treatment and prevention of gastrointestinal infections caused by enteric pathogens such as rotavirus, *Escherichia coli* or *Vibrio cholerae* in susceptible individuals including those with immunodeficiency diseases and patients with bone marrow transplants. There is also a suggestion that such agents may be useful in preventing chemotherapy-induced gastrointestinal mucositis.

Future opportunities for research include the design of oral dosage forms of antibodies which resist proteolysis and can deliver a greater fraction of immunoreactive antibody locally in the gastrointestinal tract for the treatment of infections or perhaps even to allow the absorption of antibodies for the treatment or prevention of systemic conditions.

Antibodies are immunoglobulin molecules with exquisite specificity for binding and inactivating potentially toxic or antigenic molecules which invade the body. Due to their high specificity, antibodies (particularly monoclonal antibodies) have been investigated as:

- targeting agents for cancer diagnosis and therapy[1]
- to inactivate toxic substances including drugs[2]
- as passive immunotherapy for neoplastic[3] or infectious diseases.[4]

In the vast majority of cases, these immunoglobulin molecules have been administered systemically by the intravenous route. This route was selected on the assumption that immunoglobulin molecules administered orally would be likely to become degraded and inactivated by proteases in the stomach and intestine.

However, research in this area has suggested that a fraction of orally administered immunoglobulins may retain neutralising activity, at least locally in various segments of the gastrointestinal tract, and that there may even be some absorption of these molecules, particularly in the case of infants. There is, therefore, a developing interest in designing dosage forms of immunoglobulins which could be administered orally for the treatment of infections[4] and other local conditions in the gastrointestinal tract.[5] Oral dosage forms of antibodies would have the advantages of reduced cost and simplicity of administration as well as the potential for treating localised conditions in the gastrointestinal tract.

This review focuses on the issues relating to the pharmacokinetics of orally administered immunoglobulins and speculates on the future possibilities for the oral administration of these agents.

1. Proteins and the Normal Physiology of the Gastrointestinal Tract

Orally administered proteins and peptides are subject to denaturation at the acidic pH of the stomach as well as degradation by proteases present in the stomach, small intestine and, to a lesser extent, the colon. The magnitude of the degradation in each section of the gastrointestinal tract depends on the conditions and duration of exposure, which is in turn determined by the transit time. Transit times, pH gradients and the presence of specific proteases in each section of the gastrointestinal tract are shown in table I.

The pH of gastric fluid is 1 to 3.5 in both children and adults because of the secretion of hydrochloric acid by the parietal cells.[6] However, in neonates gastric fluid has a pH near neutral at term, which rapidly decreases to pH < 3 within a few hours.[7] Milk feeding in neonates can restore gastric pH to 4 to 5.[7,8]

The chief cells of the stomach secrete the proenzyme pepsinogen, which autocatalytically digests itself, releasing the active proteolytic enzyme pepsin.[6] Pepsin is optimally active at an acidic pH (1.8 to 3.5) and digests proteins in the stomach to polypeptides.[9] The transit time in the stomach can vary considerably but has been reported to range from 0.5 to 4.5 hours with a median of 1 to 1.5 hours.[10,11]

In both adults and children the pH of the small intestine ranges from 6.3 to 7.5, whereas in the colon it is 7.5 to 8.[11,12] Proteases are more abundant in the small intestine than in the colon.[7,11] In the former, they may be present as secreted pancreatic enzymes in the lumen or associated with the enterocyte on the brush border or in the cytoplasm of the cell.[7,13]

Enterokinase (also known as enteropeptidase)

is a brush border enzyme, which is released into the lumen by the action of bile acids.[13] Enterokinase cleaves the proenzyme trypsinogen, releasing the active form trypsin. Trypsin then activates other pancreatic proenzymes (including trypsinogen), producing a mixture of various proteases including trypsin, chymotrypsin, elastase and carboxypeptidase A and B.[7,13] These enzymes degrade proteins to dipeptides, tripeptides and other small peptides as well as single amino acids which can then be absorbed by the enterocyte.[13] The brush border of intestinal epithelial cells also contains proteases (including enterokinase) and these are thought to function in both a protective and a digestive role, by proteolytically inactivating toxic or antigenic macromolecules before absorption.[14]

The pancreatic proteases and enterokinase have pH optima which are neutral or slightly alkaline.[7] Carboxypeptidase, chymotrypsin and elastase levels in the intestine are lower in neonates than in older children or adults.[7] The transit time in the small intestine ranges from 1 to 4 hours.[11]

Peptides resulting from the degradation of proteins by intestinal proteases may be endocytosed by the enterocyte after binding to specific receptors on the cell surface[6,13,14] (fig. 1). The phagosomes containing the peptide fuse with lysosomes inside the cell to form phagolysosomes, where additional proteases then degrade the peptide into its constituent amino acids.[13] The carbohydrate moiety on glycoproteins such as immunoglobulins can be degraded by lysosomal hydrolases.[7] In some cases, however, small amounts (1 to 5%) of biologically active peptides[14-16] as well as other macromolecules such as albumin[17] and immunoglobulins[18,19] may be phagocytosed by the enterocyte, escape complete digestion by intracellular proteases and reach the circulation by exocytosis on the basolateral surface of the cell.

The intestinal absorption of intact immunoglobulins may be increased in neonates[20] because of a nonspecific permeability of the intestine to various macromolecules, but this markedly decreases as the intestinal epithelium matures, a process referred to as 'closure'.[18] Nevertheless, small amounts of macromolecules may reach the circulation through binding to Peyer's patches, which are small areas of lymphoid tissue in the intestine, thought to be important for processing potentially antigenic substances in the diet.[14]

Table I. Physiological characteristics of the gastrointestinal tract related to immunoglobulin and peptide degradation

Site	pH	Protease activity	Transit time (h)
Stomach	1-3.5	Pepsin	0.5-4.5
Small intestine	6.3-7.5	Enterokinase, trypsinogen, trypsin, chymotrypsin, elastase, carboxypeptidase A and B, intracellular peptidases, lysosomal hydrolases	1-4
Colon	7.5-8	Insulinase, bacterial proteases	8-16

Macromolecules absorbed via Peyer's patches are transported to the systemic circulation in the mesenteric lymph.[11] Because of the lower levels of proteases present, the degradation of proteins and peptides in the colon is not believed to be as important as that in the small intestine, although degradative enzymes for certain biologically active peptides have been found (e.g. insulinase).[7] Bacterial proteases present in the colon may also degrade proteins.[7,13] Bacterial flora increase from $<10^3$ organisms/g in the stomach, duodenum, jejunum and upper ileum to between 10^5 and 10^7 organisms/g in the distal ileum and to between 10^{10} and 10^{13} organisms/g in the colon.[11] Immunoglobulin molecules reaching the systemic circulation would undergo hepatic extraction through binding to Fc receptors in the liver.[1]

2. Pharmaceutics and Pharmacokinetics of Orally Administered Immunoglobulins

2.1 Degradation of Immunoglobulins: *In Vitro* Studies

The use of orally administered immunoglobulins to treat local conditions in the gastrointestinal tract only requires that the molecule remain immunoreactive until it reaches the site of action.

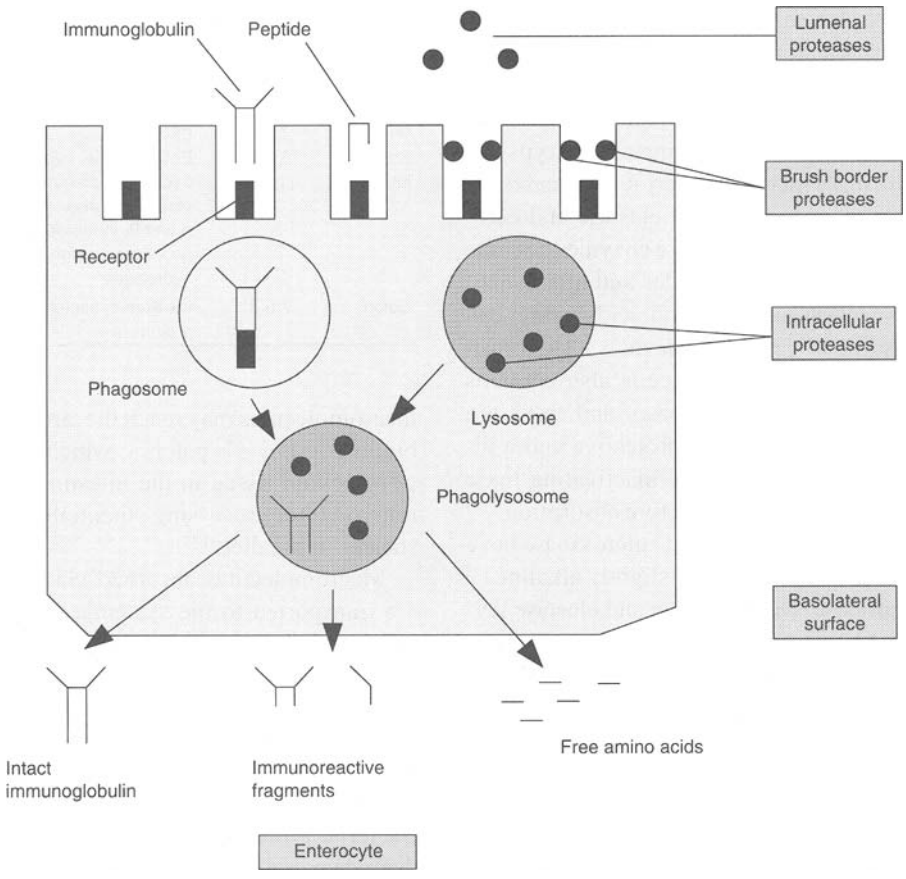

Fig. 1. Absorption of peptides or immunoglobulins by the enterocyte in the small intestine. Peptides resulting from proteolysis in the lumen (or in neonates, intact immunoglobulins) bind to specific receptors on the lumenal surface of the enterocyte. The enterocyte then phagocytoses the peptide (or immunoglobulin) into a phagosome. The phagosomes fuse with lysosomes inside the cell to form phagolysosomes, where additional proteases degrade the peptide into its constituent amino acids. Immunoglobulins may be protected from intracellular degradation by binding to a receptor. Free amino acids and small amounts of intact immunoglobulins in neonates are exocytosed on the basolateral surface of the enterocyte into the intercellular space for absorption into the systemic circulation.

However, in order for orally administered immunoglobulins to treat systemic conditions, they must reach the circulation and, therefore, must reach the distal portions of the gastrointestinal tract without undergoing any denaturation or proteolysis which would compromise their immunological activity.

Several investigators have studied the effects of gastrointestinal proteases and acidity on immunoglobulin structure and activity *in vitro* in order to predict their fate when administered orally.[8,21-23] Immunoglobulins were incubated with pepsin at pH 2 to 4 and trypsin at pH 8 in order to simulate the gastric and duodenal phases of digestion, respectively. In some experiments, trypsin was also combined with chymotrypsin[8] or other pancreatic enzymes such as carboxypeptidase and elastase.[21]

When incubated with pepsin or trypsin *in vitro*, immunoglobulins have been shown to undergo proteolysis accompanied by decreases in immunological activity. In one study[21] bovine milk immunoglobulins incubated with pepsin at pH 2 underwent extensive proteolysis with a 96% decrease in neutralising titre. When the immunoglobulin preparation was incubated with a mixture of trypsin,

chymotrypsin, carboxypeptidase and elastase at pH 7.5 following pepsin digestion, the degree of proteolysis increased 3-fold and the neutralising titre decreased by 99%. Similarly, when an immunoglobulin preparation isolated from hen eggs was incubated with pepsin at pH 2, virtually none of the neutralising activity was retained.[8] Sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE) analysis of the pepsin digest revealed that the immunoglobulins were degraded to small peptides. However, SDS-PAGE analysis of trypsin and chymotrypsin digests at pH 8 showed the presence of intact heavy and light chains and other peptides of intermediate molecular weights. Furthermore, trypsin and chymotrypsin reduced the neutralising titre to only 39 to 80% and 41 to 71% of that originally present, respectively. Similarly, Hilpert et al.[23] found that trypsin had very little effect on the antiviral activity of bovine milk immunoglobulins, whereas pepsin at pH 2 reduced the antiviral activity to 10%. Petschow and Talbott[21] demonstrated that the combination of trypsin, chymotrypsin, carboxypeptidase and elastase without pepsin had no significant effect on the neutralising titre of bovine milk immunoglobulins, whereas pepsin caused a 96% decrease. It, therefore, appears that pepsin has a greater degradative effect on proteins than intestinal proteases.

Immunoelectrophoresis has shown that a portion of the immunoglobulin molecules can remain intact in pepsin and trypsin digests but there is considerable cleavage into Fc, Fab, and $F(ab')_2$ fragments.[22,23] However, such digests can still exhibit some neutralising activity as Fab and $F(ab')_2$ fragments retain the antigen binding domain. The ratios of enzyme/immunoglobulin and duration of exposure in various segments of the gastrointestinal tract may also affect the extent of proteolysis of immunoglobulins.[8,23-25]

It has been observed that pH also affects the structural conformation and neutralising activity of immunoglobulins, particularly in the presence of pepsin at pH < 4. A consistent decrease in neutralising activity was observed when bovine milk immunoglobulins were exposed to conditions of increasing acidity from pH 7 to pH 2.[21] Similarly, immunoglobulins prepared from hen egg yolks showed a 3- to 10-fold higher loss in neutralising activity when incubated with pepsin at pH 2 (100% decrease) versus pH 4 (9 to 37% decrease).[8] SDS-PAGE profiles suggested that the extent of proteolysis was considerably less when the immunoglobulins were incubated with pepsin at pH 4 versus pH 2. However, Petschow and Talbott[21] have suggested that acidic conditions alone in the absence of pepsin can induce conformational changes in the antibody structure, which can also lead to decreases in functional activity.

Bovine milk and human serum contain predominantly IgG, whereas IgA is the predominant immunoglobulin class in human breast milk.[21,26] Although classified as an IgG-class immunoglobulin, the predominant immunoglobulins from hen egg yolks are structurally different from mammalian IgG, and are classified as IgY (yolk immunoglobulin).[27] Immunoglobulins of different classes appear to exhibit different characteristics with respect to proteolysis and conformational damage due to acidic conditions. IgA in human milk may be protected from proteolysis by binding to secretory component.[7,28]

In one study, secretory IgA was found to resist proteolytic digestion.[26] Shimizu et al.[25] demonstrated that IgY was slightly less stable than bovine IgG to pepsin digestion and acidity but was relatively stable against trypsin and chymotrypsin. Hatta et al.[24] and Shimizu et al.[27] found IgG to be more stable than IgY at high temperatures (>70°C) and under very acidic conditions (pH 2 to 3).

2.2 Pharmacokinetics of Orally Administered Immunoglobulins

As described in section 2.1, the results from *in vitro* studies suggest that a proportion of immunoglobulin molecules may retain at least partial immunological activity when subjected to proteolytic conditions. This also appears to be the case *in vivo*, as stool samples from infants administered bovine milk immunoglobulin[23,29] or human serum

immunoglobulin orally were found to contain immunologically active IgG.[26] Hilpert et al.[23] reported that orally administered immunoglobulins recovered in infant faeces retained up to 10% neutralising activity. Losonsky et al.[30] also detected the presence of immune complexes of orally administered IgG and rotavirus antigen in infant stool samples.

In adults, Roos et al.[31] found that 19% of orally ingested IgG was still immunologically active after passing through the ileum. The IgG recovered from the ileum was degraded to $F(ab')_2$ fragments. Other studies have shown that up to 50% of orally administered immunoglobulins can be recovered in infant or adult stool.[26,29,30] The immunoglobulins recovered were in the form of Fc, Fab, and $F(ab')_2$ fragments due to proteolytic digestion by gastric and pancreatic enzymes.[23,26,29]

The normal physiological fate of ingested proteins in the adult is degradation by proteolytic enzymes to small peptides and amino acids which are subsequently absorbed. It is not unexpected then that orally administered immunoglobulins should undergo the same process and, therefore, not be available in intact form for absorption. Although very small amounts (<5%) of intact immunoglobulins may reach the systemic circulation,[18] for the most part these proteins are degraded by gastric and intestinal proteases.

Blum et al.[26] fed human serum immunoglobulins (100 to 800 mg/kg/day for 5 days) to 6 immature infants ranging from 4 to 13 weeks old in order to evaluate the *in vivo* fate of orally administered antibodies. No increase in serum concentrations of the intact immunoglobulin were observed, suggesting very poor absorption. In another clinical trial[28] infants were fed an IgA-IgG preparation (600 mg/day for 28 days) to assess the efficacy of oral immunoglobulin administration in lowering the incidence of necrotising enterocolitis. Again, no increase in serum IgA or IgG levels was observed.

Losonsky et al.[30] evaluated the pharmacokinetics of orally administered human serum immunoglobulins incorporating a biotinylated-^{125}I-immunoglobulin tracer in 2 children aged 4 years and 16 months, both with an immunodeficiency disease. The proportion of total recovered radioactivity distributed in the stool (48 to 49%), urine (48 to 49%) and serum (2 to 4%) were similar for both children. Only 0.01% of the radioactivity present in the urine was in a high molecular weight form as determined by ammonium sulphate precipitation. Similarly, in the blood none of the radiolabel was in a high molecular weight form. This suggests degradation of the immunoglobulins in the lumen of the intestine or in enterocytes, with subsequent absorption of radioiodinated peptides or free radioiodine. Approximately 50% of the radioactivity in the stool was in a high molecular weight form.

Although there appears to be little systemic absorption of intact immunoglobulins through the human gastrointestinal tract, recent immunohistochemical studies in mice administered human IgG antibodies orally have nevertheless shown that antibodies can penetrate the epithelium and muscularis mucosa of the intestine.[5] Interestingly, intestinal epithelium in the proximal intestine of suckling rodents and other mammals is reported to express Fc receptors which could facilitate the transport of IgG across the epithelial membrane and into the systemic circulation through a process termed transcytosis.[32] The amount of time for which immunoglobulins are exposed to acidic and proteolytic conditions in the stomach and small intestine before reaching the distal portions of the gastrointestinal tract may determine the extent of survival of intact forms of the immunoglobulin.[26] The transit time for orally administered immunoglobulins in the gastrointestinal tract of infants and children is reported to range from 12[30] to 36[23] hours.

Certain classes of immunoglobulins, such as IgA and IgY, appear to be more resistant to proteolytic degradation than other classes (see section 2.1) and, therefore, have some advantages for oral administration. The amount of immunoglobulin administered orally may also have an effect on the fraction absorbed, particularly if the degradative pathways are dose-limited. However, Blum et al.[26] have found a linear relationship between the dose of immunoglobulins administered and the amount

recovered in the stool, suggesting that higher doses may not improve absorption. However, some investigators[21] have suggested that more than 3 g/day of orally administered immunoglobulins may be necessary to achieve viral neutralising capability locally in the gastrointestinal tract. The neutralising titre of the immunoglobulins is also an important factor.[23]

2.3 Pharmaceutics of Orally Administered Immunoglobulins and Peptides

Research has been focused on developing oral dosage forms of immunoglobulins which would protect against the proteolytic and denaturing conditions of the gastrointestinal tract. In one approach, Shimizu et al.[33] encapsulated IgY antibodies in egg lecithin/cholesterol liposomes in order to stabilise the antibodies against hydrolysis by pepsin or acidic conditions. The stability of liposomal IgY against pepsin hydrolysis and acidic conditions was increased, suggesting that liposomal encapsulation may protect immunoglobulins from degradation in the stomach. Once within the bile salt–rich region of the small intestine, the liposomes would degrade, thus releasing the IgY antibodies. Since IgY has been shown to be fairly stable against trypsin and chymotrypsin,[25] the released antibodies could passively immmunise the gastrointestinal tract and protect it from infection by bacteria or viruses.

More recently Shimizu and Nakane[34] attempted to encapsulate IgY antibodies in a water/oil/water (W/O/W) emulsion. However, the emulsification process caused considerable denaturation of the IgY, resulting in only 16% of the antibody activity remaining after encapsulation. Surface denaturation of the antibody was attributed to absorption to the oil/water interface due to hydrophobic interactions between the oil and hydrophobic regions on the antibody. However, antibody inactivation was decreased when a small concentration of 'Tween 20' was added, which may preferentially absorb on to the oil/water interface, inhibiting antibody adsorption.

Using a simpler approach, Petschow and Talbott[21] attempted to protect bovine milk immunoglobulins from degradation by gastric and duodenal enzymes, by formulating them in the presence of skim milk. The hypothesis was that the presence of other proteins in the skim milk would competitively inhibit the degradation of the immunoglobulins, but unfortunately this did not prevent degradation.

Proteins and peptide drugs could be coated with azopolymers, which protect against proteolytic digestion in the stomach and small intestine but are degraded in the colon by microbial azoreductases, releasing the free drug for absorption.[11] Released macromolecules could be absorbed by M-cells on Peyer's patches which exhibit pinocytic activity.[11] This may be a good route of absorption of immunoglobulins and peptide drugs in children and young adults, but may be less useful in older adults because of a decrease in the size and number of Peyer's patches.[11,35] Modifications of the structure of proteins and peptides may also improve the resistance to proteases and allow greater absorption. Proline-containing peptides,[36] those with a blocked N terminus[14] or with D-amino acids,[16] may be more resistant to proteolysis.

2.4 Genetic Engineering of Immunoglobulins

Secretory IgA play a major role in protecting the mucosal membrane from attack by micro-organisms. These locally produced antibodies do not activate complement and, therefore, do not attract inflammatory phagocytic cells. However, the secretory IgA response is usually short-lived and is difficult to boost. The use of genetically engineered IgA antibodies of appropriate specificity towards the infectious agent may be suitable for passive immunotherapy.

Although mouse monoclonal antibodies have been available for several years, their use in human immunotherapy has been restricted due to the human anti–mouse antibody (HAMA) response.[1,37] Circulating antibodies directed against the variable (anti-idiotypic) and constant (anti-isotypic) regions of the mouse monoclonal antibody develop within 2 weeks of administration and can persist

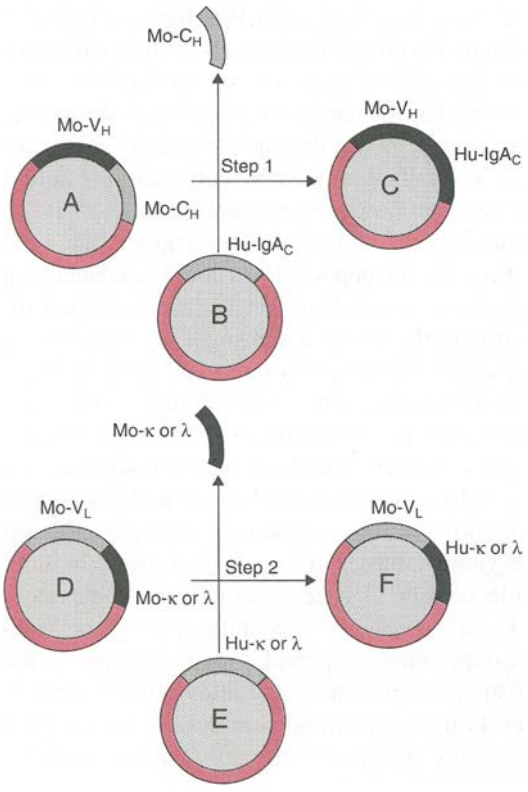

Fig. 2. The construction of a chimaeric IgA antibody. Construction of the heavy chain is shown in step 1. Plasmid A consists of DNA coding for the mouse antibody heavy chain variable domain (Mo-V_H) and constant domain (Mo-C_H). The Mo-C_H DNA is removed from plasmid A and replaced with the DNA coding for the human IgA constant domain (Hu-IgA_C) from plasmid B. This generates plasmid C which consists of DNA sequences for the chimaeric antibody heavy chain. Construction of the light chain is shown in step 2. Plasmid D consists of DNA coding for the mouse antibody light chain variable domain (Mo-V_L) and constant domain which could be either Mo-κ or λ. The Mo-κ or λ DNA is removed from plasmid D and replaced with the DNA coding for the human κ or λ (Hu-κ or λ) constant domain from plasmid E. This generates plasmid F which consists of DNA sequences for the chimaeric antibody light chain. Plasmids C and F when transfected into a rat myeloma cell line can secrete the chimaeric antibody (designed by Robin Sandhu).

for several months.[1] HAMA binds and inactivates the mouse monoclonal antibody in the circulation and the resulting immune complexes are sequestered by the reticuloendothelial system. To overcome these limitations, human monoclonal antibodies have been made, but chimaeric antibodies consisting of mouse variable (V) domains and human constant (C) regions may in fact be more suitable for treating human gastrointestinal tract disease.[38]

Using the technique of antibody phage display library[39] it is possible to screen for high affinity antibodies which neutralise pathogens or their toxins which damage the gastrointestinal tract. The phage displays the antibody on its surface and the DNA coding for the antibody V-domain is inside the phage. To make these antibodies suitable for passive immunisation of the gastrointestinal tract, it is possible to construct IgA or IgM isotype monoclonal antibodies. IgA and IgM antibodies represent the main immunoglobulin populations in the gastrointestinal tract. DNA coding for the V-domain can be obtained from the antibody phage display and the DNA coding for the various human antibody isotypes have been cloned and sequenced.

Genetic engineering techniques allow construction of chimaeric antibodies as shown in figure 2. Chimaeric antibodies consist of mouse V-domains and human C regions and thus would have the human effector functions, but mouse V-domain specificity. The C region amino acid sequence of the chimaeric antibody may be modified further by site-directed mutagenesis[40] to resist protease degradation in the gastrointestinal tract and increase stability.

3. Clinical Applications of Orally Administered Antibodies

As described in section 2, there is evidence to indicate that a fraction of orally administered antibodies can survive passage through the human gastrointestinal tract and retain structural characteristics and immunological activity. This raises the possibility of treating gastrointestinal infections by passive immunisation using orally administered immunoglobulins.

Gastrointestinal infections are important causes of morbidity and mortality, particularly in underdeveloped nations. Passive immunisation is currently under experimental and clinical evaluation, and results so far are encouraging. A comprehensive review of the clinical applications of passive immun-

isation and the theoretical and practical considerations of the approach is beyond the scope of this article; however, several studies are highlighted below. For a detailed review the reader is referred to the article by Hammarstrom et al.[41]

Infectious agents such as rotavirus, *E. coli*, *V. cholerae*, *Clostridium parvum* and *Helicobacter pylori* are known to cause gastroenteritis. Severe diarrhoea is a major complication and, if untreated, is life-threatening. Evidence seems to indicate that gastroenteritis of any viral origin may be treated by passive immunisation and may not necessarily require antibodies specific for the infectious agent.

In a double-blind, placebo-controlled, randomised trial, Guarino et al.[4] successfully treated rotavirus-induced diarrhoea in infants using a nonspecific human serum immunoglobulin preparation. In the group of treated infants, the duration of diarrhoea and duration of hospital stays was lower by 42 and 38%, respectively, compared with untreated infants. In addition, the shorter duration of diarrhoea was associated with a shorter length of time during which rotavirus was present in the stool.

Similar results were also reported by Hilpert et al.[23] who used rotavirus-specific immunoglobulins isolated from bovine colostrum rather than nonspecific immunoglobulin to treat cases of infantile gastroenteritis. Other studies have also suggested that oral administration of immunoglobulins may be effective against infantile gastroenteritis.[42,43]

In other reports, several HIV-infected patients with *C. parvum*-induced diarrhoea were successfully treated with specific bovine colostral immunoglobulin.[4,44,45] Those who are predisposed to gastrointestinal infections, such as children and adults with severe immunodeficiency diseases[30] and recipients of bone marrow transplants,[46] may also benefit from passive immunisation. Interestingly, the degradation of immunoglobulins in the gastrointestinal tract of patients with bone marrow transplants is impaired because of the destruction of the gastrointestinal mucosa resulting from the preparative regimen, a high gastric pH, rapid intestinal transit, limited oral intake and antibacterial therapy which reduces bowel flora.[46,47]

Necrotising enterocolitis, a condition of the gastrointestinal tract which occurs predominantly in premature and low birthweight infants, is a life-threatening illness associated with a mortality rate of 10 to 30%.[48,49] In a randomised controlled clinical trial in 1988,[28] administration of a human serum IgA-IgG preparation reduced the incidence of necrotising enterocolitis in premature infants. Further evidence that IgA may be important in protecting against necrotising enterocolitis was demonstrated in a multicentre, prospective study which found an association between breast feeding and a lower incidence of necrotising enterocolitis in low birthweight infants.[50] Evidence suggests that immunoglobulins may have an anti-inflammatory as well as an antiviral effect in their prevention of necrotising enterocolitis by down-regulating the release of inflammatory mediators such as tumour necrosis factor α and interleukin 6.[51]

One novel application proposed for the orally administered immunoglobulins is the treatment of gastrointestinal mucositis, a toxic adverse effect of chemotherapeutic drugs, such as anthracyclines.[5] Morelli et al.[5] investigated the feasibility of treating intestinal mucositis in BALB/c mice administered doxorubicin, using the monoclonal antibody MAD11 which binds and inactivates the drug. Myelosuppression and gastrointestinal mucositis are dose-limiting adverse effects associated with doxorubicin.[52] Oral administration of MAD11 reduced both weight loss and mortality in doxorubicin-treated mice and reduced the extent of doxorubicin-induced apoptosis of intestinal cells.

The mechanism of reduced mucositis with the MAD11 antibodies is not clear, but the antibodies were able to penetrate as deep as the muscularis mucosa of the small intestine, which may have resulted in neutralisation of the doxorubicin in intestinal tissue. There is also the possibility that the MAD11 antibodies neutralised doxorubicin or its metabolites excreted via the biliary system into the lumen of the small intestine.

Oral administration of immunoglobulins is generally well tolerated. Reported adverse effects include abdominal cramps, nausea and vomiting[44,53] but in most cases no adverse effects were observed. Allergic reactions to bovine milk– and egg-derived immunoglobulins are possible.[53] HAMA may develop in patients administered murine immunoglobulins.[1]

4. Conclusions

Although orally administered immunoglobulins are susceptible to degradation by proteolytic enzymes in the gastrointestinal tract, research has shown that a fraction of the administered dose retains some immunological activity, and, therefore, these agents may be useful for the treatment or prevention of local infections by enteric pathogens in susceptible individuals. Future opportunities for research include the development of protease-resistant oral dosage forms, either to increase the fraction of immunoreactive antibody delivered locally in the gastrointestinal tract or to allow systemic absorption.

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Errata

Vol. 31, No. 3, page 192: In columns 7 and 9 of Table II the units should read μ*g/L* and μ*g/L* • *h* respectively, not mg/L and mg/L • h as printed.

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