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Conversion of mg per cent to µmol/l (based on formula supplied by S.A.I.M.R.)

\[
\begin{align*}
\text{mg\% lecithin} & \quad \times 13.7 = \text{µmol/l lecithin} \\
\text{mg\% lysolecithin} & \quad \times 20.02 = \text{µmol/l lysolecithin}
\end{align*}
\]

Page numbers in thesis and appendices referring to amounts of lecithin and lysolecithin:


Appendices:

A, B, C, D, E, F, G, H, I, J.
1. INTRODUCTION

Reflux of bile into the stomach was first reported by J. Hunter almost two centuries ago, and later by Beaumont in 1883 (1). Little attention was paid to this phenomenon until 1914, when Boldyreff (2), and slightly later Hicks, in 1915, and Spencer in 1916 (3,4), suggested that duodenogastric reflux could be a protective mechanism against the effect of acid in the gastric juice. However, MacLean (5) in 1928, showed that duodenogastric reflux was not a significant factor in the regulation of gastric acidity, so the phenomenon was ignored by most investigators. Later, the interest in duodenogastric reflux was revived, when Schindler in 1947, suggested that the regurgitated bile salts had a damaging effect on the gastric mucosa. This view was supported by Grant et al in 1951 (6) and Palmer in 1954 (7). Later, Du Plessis (8-10) in a study based on clinical and histological observations, suggested that duodenogastric reflux caused atrophic gastritis and subsequently gastric ulceration. In 1964 Lawson (11) produced gastritis in dogs, by directing the duodenal contents into the stomach. More studies supported the injurious effect of the duodenal contents on the gastric mucosa, and today this is a generally accepted assumption (12-22).

Various studies have been performed to isolate the injurious agents in the duodenal contents. Lawson showed that a mixture of bile and pancreatic juice caused more gastritis than either of the two components separately (23). Other studies suggested that the injurious effect of duodenal juice was due to its lysolecithin content, a substance formed from lecithin by the action
of the pancreatic phospholipase A, in the presence of trypsin and taurocholic acid (24-28).

The occurrence and effect of duodenogastric reflux depend on many factors, such as gastric and duodenal motility (29-31), anatomical and functional conditions of the pylorus (31-34), hormonal factors (35-39) and the presence of certain food substances (12,40). Recently, some studies based mainly on retrospective clinical findings, suggested that after cholecystectomy there was increased bile reflux into the stomach (41-46). The theory behind this assumption was that during fasting bile was stored in the gall bladder, and was later excreted into the duodenum during food intake. If there was no gall bladder reservoir, presumably the bile would flow continuously into the duodenum, and if the conditions were favourable, reflux into the stomach could occur. If this is true, some of the so-called 'post-cholecystectomy syndrome' cases might be the result of increased bile reflux. However, Earlam (47,48) suggested that increased bile reflux associated with gall bladder disease, usually reverted to normal after cholecystectomy. He postulated that in the presence of a non-functioning gall bladder or after cholecystectomy, bile flowed into the duodenum in a thin and unconcentrated form, therefore bile reflux was less. Lee (49) reported no correlation between cholecystectomy and gastric pathology. Taylor (43) analysed retrospective clinical data and found that the combination of truncal vagotomy and pyloroplasty together with cholecystectomy, was associated with a higher incidence of bile reflux gastritis, than truncal vagotomy and pyloroplasty alone.
2. THE OBJECT OF THE PRESENT STUDY

The object of the present investigation was to study the possible relationship between cholecystectomy and bile reflux into the stomach, under different experimental conditions.
3. REVIEW OF THE RELEVANT LITERATURE

3.1 Physiology of duodenogastric reflux (D/G reflux)

Duodenogastric reflux seems to be the result of a disturbance of either the motility or the pressure profile at the gastro-duodenal junction - the antrum, pylorus and the duodenum. Several experimental studies, involving pressure recordings, cineradiography and electrical activity measurement (31, 50-53) support the general belief, that normally there is a co-ordination of the motility of the three components of the gastro-duodenal junction. Duodenogastric reflux may occur if this co-ordination is disturbed for any reason - anatomical, hormonal, neurogenic, or chemical. Braithwaite (54) suggested that reflux would occur when the intraduodenal pressure was higher than that of the stomach, and that the pylorus would be forced open by a high intraduodenal pressure. He pointed out that during fasting or a fatty meal, the pressure gradients favour reflux.

Duodenal peristalsis is controlled by a pacesetter potential which is situated within an area 1 cm distal to the pylorus (55). It has a pace rate of 11 cycles/min. and imparts at a velocity of 200 mm/sec. (56, 57). Eighty-five out of 100 proximal duodenal peristaltic contractions will occur after a gastric peristaltic wave (58, 59). Code (60) suggested that abnormal electrical activity at the duodenum may precipitate reflux. Munk (31) in experiments in dogs, showed that an ectopic duodenal pacemaker could produce retrograde peristalsis, leading to a duodenogastric reflux.
gastric reflux. If the duodenal pacemaker were within 5-6 mm of the gastro-duodenal junction, there would be no reflux, because the pylorus closes before reflux occurs. However, when the ectopic pacemaker is more distal the pylorus is unable to close in time, and reflux occurs. Kelly et al. (61), pacing the distal duodenum of dogs at a higher rate than normal, showed that this favoured reflux.

3.1.1 The pylorus and reflux

Although most investigators agree about the significance of gastro-duodenal junction motility in duodenogastric reflux, much controversy still exists concerning the role of the pylorus. Many authors give the pylorus a minor passive role in preventing reflux. Menta (62) used a circumferential pressure sensitive transducer assembly, and failed to demonstrate a high pressure zone in man or the dog. Many other authors recorded similar results (63,64).

However, other investigators suggest a more active role for the pylorus (65). A number of studies have shown pyloric relaxation during antral contraction (66), and a high pressure zone, which is positively affected by the injection of secretin or cholecystokinin (CCK) and by intraduodenal fat, aminoacids, acids and glucose (36,50,66,67). Isolated circular muscle from the human pylorus has shown specific properties absent from adjacent muscle. These properties include non-cholinergic inhibitory
innervation (68). Forgerson (65) suggested that reflux was prevented during the contraction of the duodenal bulb, by contraction of the duodenal part of the pyloric sphincter.

Rothmud et al. (69) showed that after pyloroplasty there was increased reflux and gastritis. Several other authors supported this view (34,43). However, other investigators found no increased reflux after pyloroplasty (70,71). Kilby (72) even suggested that surgical procedures involving the pylorus, reduced the quantity and force of reflux. He suggested the explanation that the quantity of reflux was significantly determined by the contraction of the duodenal cap. If the pumping effect of the cap was abolished by means of a pyloroplasty, the ability of the proximal duodenum to cause reflux was reduced. Sonnenburg (73) and Munk (74) showed in animals, that D/G reflux depended more on the contractile pattern on either side of the pylorus than on the diameter of the pyloric ring itself.

3.1.2 Gastric emptying and D/G reflux

The damaging effect of the refluxed duodenal material on the gastric mucosa, depends more on the speed of gastric emptying (contact time between the cytotoxic agents and the mucosa), than on the amount of reflux (33,75,76). The gastric fundus may play an important role, since it regulates the gastric emptying of fluids. Certain factors influencing gastric emptying will be briefly reviewed:
3.1.2.1 Hormones

Gastrin (36,77), secretin and CCK (33,78-83) all delay gastric emptying.

3.1.2.2 Pylorus

Controversy still exists concerning the role of the pylorus in regulating gastric emptying. Capper (64) stated that "the pylorus is not a sphincter in the same sense that the anus is a sphincter, i.e. it does not close the lumen and keep it closed with a brief relaxation to allow chyme to pass through. Rather, it is normally open and closes only to prevent regurgitation of duodenal contents during the brief powerful systole of the duodenal cap".

Some studies suggest that the pylorus has no control over gastric emptying (85). Stemper et al (32) found that when the pylorus was kept open by means of a Teflon tube, the rate of gastric emptying of fluids was not increased. However, some authors, using barium studies, suggested that antral mucosa 'herniates' into the pylorus with a plug effect (86,87). If this is true, introduction of a tube into the pylorus may impair this function. Many investigators found that after pyloroplasty there was no increase in the rate of gastric emptying (69,70,88). Others reported the opposite (70,89). Lawaetz et al. (88) believe that the effect of pyloroplasty, when associated with a vagotomy, is influenced by the type of vagotomy. A few authors even reported that pyloroplasty slows down the emptying of liquids (90).
3.1.2.3 Vagotomy

3.1.2.3.1 Physiology

The rate of gastric emptying depends on the pressure gradient between the stomach and the duodenum, and the resistance of the pylorus to the flow of chyme (91-93). The proximal stomach is especially important in the control of intragastric pressure and gastric emptying, because of the two properties of receptive relaxation, and accommodation to distension (94) both being regulated by the vagus. The stomach can be distended from 300 mls to 1000 mls with minimal increase in intraluminal pressure (92). The proximal stomach regulates the emptying of liquids (94). The distal stomach acts as a mixer and grinder, and regulates the emptying of solids (94). The motility is controlled by the vagus.

3.1.2.3.2 Highly selective vagotomy (HSV) and gastric emptying.

Denervation of the proximal stomach results in loss of receptive relaxation and accommodation to distension (94-97). This leads to high pressures during gastric filling, and rapid emptying of liquids (94,98). Since the innervation of the distal stomach is preserved, the emptying of solids is not affected (94). Initially, gastric emptying after HSV was reported as being normal (99,100). Later studies, however, showed a rapid emptying of liquids (94,101). Cleysten (70) reported a fast emptying of
liquids in the first 10 minutes, after HSV or truncal vagotomy. Clark and Alexander-Williams (101) found that the initial fast gastric emptying during the first 10 minutes persisted 12 months after HSV. The normal pattern of emptying after the initial 10 minutes was not lost. Similar results were reported by other investigators (102-104). Faxen and Kewenter (103) reported that the final emptying time was unchanged after HSV. Other studies support this finding (104).

3.1.2.3.3 Truncal vagotomy (TV) and gastric emptying

TV has the same effect on the proximal stomach, and therefore the same pattern of gastric emptying of liquids occurs as with HSV (16,88,89,99). Lawaetz et al. (88) showed in dogs, that TV increased the initial gastric emptying, but not the 60 minute period of emptying. After pyloroplasty was added, no change occurred in the pattern or the 60 minute period of emptying. However, Clark and Alexander-Williams (105) believe that pyloroplasty accentuates the emptying effect in any of the 3 types of vagotomy. Other reports support this concept (90).

The main difference between HSV and TV, is that the latter denervates the distal stomach and bowel. The denervation of the antrum results in weak peristalsis, and slowing of emptying of solids (106). It is to avoid the stasis of solid particles of food that a drainage procedure is necessary after TV.
3.1.2 Other factors and gastric emptying

Hypertonic or hypotonic solutions delay gastric emptying (107, 108) as do acid solutions and fat (109, 110). Barber et al (111), using solids labelled with indium and liquids with $^{57}$Cr, showed that a mixture of solids and liquids empties more slowly than liquids only.

3.2 Cholecystectomy and biliary system changes

3.2.1 Anatomy of Oddi's sphincter in man and the dog

There appears to be a marked species difference in the anatomy and physiology of the sphincter of Oddi. The embryological development of the sphincter in humans is different from that seen in dogs. In man the intramural common bile duct is encircled by only one thin layer of muscle (muscus proprius), thus it is relatively free from compression by the duodenal wall. The sphincter function and bile flow are therefore minimally affected by duodenal peristalsis and tone. In contrast to this, the intramural common bile duct of the dog is ensheathed by an outer circular layer from the tunica muscularis and an inner layer from the muscularis proprius. This results in control of bile flow, by duodenal motility and tone (112). Because of this relationship between the common bile duct and the duodenal musculature, it is likely that autonomic nerves play an important role in regulating the bile flow in dogs, but a less important one in man (112, 113).
3.2.2 Cholecystectomy and the common bile duct

Dilatation of the common bile duct after cholecystectomy was first reported in dogs by Oddi in 1887 (114), and confirmed by Judd in 1917 (115). Since then, many studies concerning the post-cholecystectomy changes of the biliary tree have been published. It seems that the changes are different in dogs and humans. It is generally accepted that the canine common bile duct dilates after cholecystectomy (115-117). Mahour et al. (116) showed that the duct in dogs reaches its maximum diameter 3 weeks after cholecystectomy, and then contracts slightly to remain about twice the pre-operative diameter. Similar results were reported by others (115,117). This change might be due to the anatomy of the intramural part of the common bile duct (2.2.1). Mahour (117) showed that there was no dilatation when the intramural duct was dissected free from the surrounding duodenum. Kyosola (118) reported the existence of a local reflex, between the gall bladder and the common bile duct. If this reflex is disrupted by means of a cholecystectomy, dilatation of the duct may occur.

Some earlier studies (119,120) suggested that the human common bile duct dilates after cholecystectomy, although later radiological and autopsy studies showed no change (121-130). Benson (131) in an autopsy study found that there was duct dilatation only in patients with the 'post-cholecystectomy syndrome', but not in symptom free cholecystectomized patients. Similar results were reported by Bodvall (132).
3.2.3 Cholecystectomy and bile

3.2.3.1 Physiology

The total bile salt pool is estimated to be 3-5 gm. It circulates 6 to 10 times per day through the enterohepatic circulation. A small amount of bile salts is lost in the stool every day. An equal amount is synthesized in the liver (133,134). In the presence of a functional gall bladder, 90% of the bile salt pool is stored in the gall bladder between meals. In the absence of the gall bladder, 85% of the bile salts are stored in the intestine (135).

3.2.3.2 Cholecystectomy and bile circulation

There is a considerable difference of opinion concerning the effect of cholecystectomy on bile salt pool size. Some authors recorded no change (136). However, other studies in man and animals showed a significant decrease (137-139). Beher et al. (140) found a decreased pool in cholecystectomized animals during fasting but no change in the fed state. It has been suggested that with an intact gall bladder, the bile salt pool circulates only when nutrients are present in the small bowel (140). In the absence of a gall bladder the pool circulates constantly (137-142).

3.2.3.3 Cholecystectomy and bile composition

It is generally accepted that bile synthesis and composition are not affected by cholecystectomy (137,140,143,144).
3.3 Truncal vagotomy and the biliary system

There is controversy about the effect of truncal vagotomy on hepatic bile flow and composition. Fletcher and Clark (145) reported that after truncal vagotomy there was no change in basal bile volume during starvation, and no effect on cholesterol or phospholipid concentration. However, the total bile salt concentration was reduced. Stempel et al (146) showed that in vagotomized patients there was no change in bile synthesis, but there was a significantly larger bile acid pool than in control subjects. Other authors reported similar findings (147, 148) and have attributed this phenomenon to increased storage capacity in the gall bladder. Bile acid pool size is dependent to a large extent on the emptying rate of the gall bladder (146, 149). Jones and Smith (150) supported the concept that truncal vagotomy had no effect on hepatic bile. During secretin stimulation they found no significant difference between pre- and post-vagotomy bile flow, bicarbonate and chloride output.

Reports on the effect of truncal vagotomy on the gall bladder are conflicting, probably because cholangiography is not an adequate method of assessing gall bladder function. Kramhoft et al (151) found no significant changes in the kinetics of the human gall bladder, after truncal vagotomy. Other investigators reported similar results (152-155). Inberg and Vuorio (154) showed that in vagotomized patients the residual volume of the gall bladder after emptying was greater than that in control subjects. Similar
findings were recorded by others (156,157). Snape (158) showed that in dogs truncal vagotomy did not affect the capacity of the gall bladder to contract, but it did prolong the latent period. The author suggested that there were 2 phases during gall bladder contraction: the initial phase which was under vagal control, and the second prolonged phase under humoral control. Malagelada et al (159) found that the gall bladder of vagotomized patients showed an increased sensitivity to cholecystokinin.

3.4 Truncal vagotomy and pancreatic secretion

Vagal stimulation results in an increased output of enzymes. Although it seems that the vagus acts directly on pancreatic acinar cells, its indirect effects may be of greater importance. Thus, vagal stimulation promotes gastric acid secretion which in turn promotes the release of secretin. Secretin causes pancreatic secretion (160).

In man and experimental animals, truncal vagotomy reduces both the basal pancreatic secretion and the response to food, acid, fat and protein in the small bowel (159,160). There are different views about the effect of secretin or cholecystokinin on the vagotomized pancreas. Some authors found decreased sensitivity of the pancreas to the hormones (159,161,162), whereas others found no significant change (163,164). These variations may be the result of species differences, techniques used, and the dose of hormones.
3.5 Bile phospholipids
3.5.1 Physiology

The main bile phospholipids are lecithin and lysolecithin. Lecithin is the only phospholipid in hepatic bile (25,165,166). It has a concentration of 1.0 - 4.3 g/lt (165). It is also found in very small quantities in plasma, erythrocytes, brain and cerebrospinal fluid. Lysolecithin is found mainly in duodenal bile, and in very small concentrations in plasma and erythrocytes (165). Lecithin is metabolized to lysolecithin by the action of the pancreatic Phospholipase A, in the presence of trypsin and taurocholic acid (167). This reaction takes place in the duodenum and upper jejunum. Sixty to 100% of the phospholipids in the upper small bowel are found in the form of lysolecithin (166). Lysolecithin may be further hydrolyzed to glycerol phosphorylcholine, by the action of a lysophospholipase. This reaction is inhibited by bile acids.

Phospholipase A is produced mainly in the pancreas, although very small quantities may be produced in other tissues. Magee et al (168) noted that both calcium ions and high concentrations (higher than 0.1 mM) of ethylenediaminetetraacetic acid (EDTA) have a strong inhibitory effect on phospholipase A. The authors recorded that optimal activation of phospholipase A occurred at a pH of 9.0. Sjödahl (169), however, found the value to be 4.5. This discrepancy might be the result of different techniques. Sjödahl et al. in a series of studies (169-171), detected the