ANALGESIA IN BILIARY PAIN*

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Biliary colic is so severe that women describe it as being worse than childbirth. In the treatment of this pain morphine is said to be contra-indicated. This is based on the thesis that morphine causes spasm of the sphincter of Oddi[1-6] and of the gallbladder.[7,8]

There is no doubt that the pain produced by a gallstone in the common bile duct may be aggravated by morphine,[4,5] and in fact morphine can produce biliary colic in the absence of gallstones,[6,9] presumably by its effect on the sphincter of Oddi. However, many older clinicians[10-12] maintain that morphine is the drug of choice in gallbladder pain.

My interest in this subject was aroused by a well-known clinical observation.[13] Patients often present with a history of repeated attacks of gallbladder pain due to impaction of a gallstone in the neck of the gallbladder. These attacks start suddenly and the pain is relieved immediately by an injection of morphine. There is no recurrence of the pain after the effect of the morphine has worn off. Four such patients admitted to our wards during the past 2 years were carefully questioned, and confirmed this observation.

The relief may be due to the central analgesic effect of the morphine,[2,5,14] but this does not explain the sudden cessation of the pain, with no aftermath or recurrence when the effect of the morphine has worn off.

It also appears to be unphysiological for morphine to produce spasm of the sphincter and contraction of the gallbladder simultaneously.[15,16] Therefore there may be another explanation for the sudden relief of pain in these cases, namely, disimpaction of the gallstone from the neck of the gallbladder – possibly due to the effect of the morphine on the biliary system.

The purpose of this investigation was to find a suitable drug to relieve biliary pain by determining the actions of various analgesics and antispasmodics on the sphincter of Oddi and the gallbladder.

PRELIMINARY INVESTIGATIONS

Preliminary investigations, which dealt with the effects of drugs on the sphincter of Oddi, have already been published[17] and will be referred to only briefly in this article. They were carried out as follows:

Material and Methods

Patients who had undergone exploration of the common bile duct with T-tube drainage were investigated. In all of them the short limb of the T-tube was at least ½ an inch away from the ampulla of Vater. The sphincter of Oddi was intact and normal in each of the patients tested.

The pressure apparatus (Fig. 1) consisted of a water manometer which was connected to the T-tube and by means of

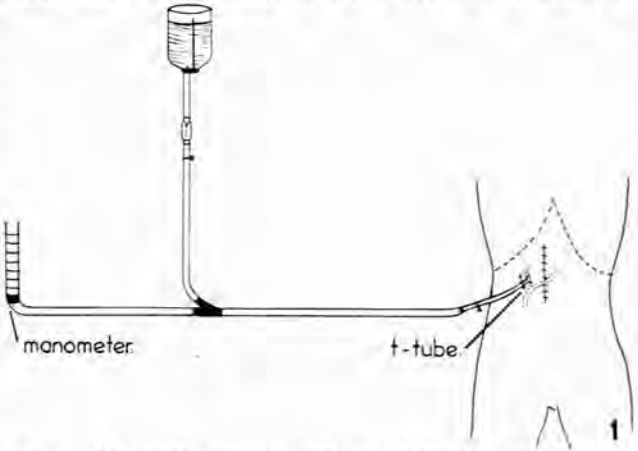

Fig. 1. The simple apparatus used for determining common-duct pressures.

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a Y-connection to a vacolitre of normal saline which was used to fill the system. The whole system was filled with saline and the drip was then clamped off.

Once the level in the manometer was constant the patient was given amyl nitrite to inhale. This relaxed the sphincter of Oddi completely and the reading on the manometer was taken as zero.

Effect of Various Analgesics

The graphs in Fig. 2 show the effect of 3 analgesics on the sphincter of Oddi. The resting pressure in graph 2A was 15 mm. of water. After inhalation of amyl nitrite the tone of the sphincter of Oddi was released and the pressure fell to zero.

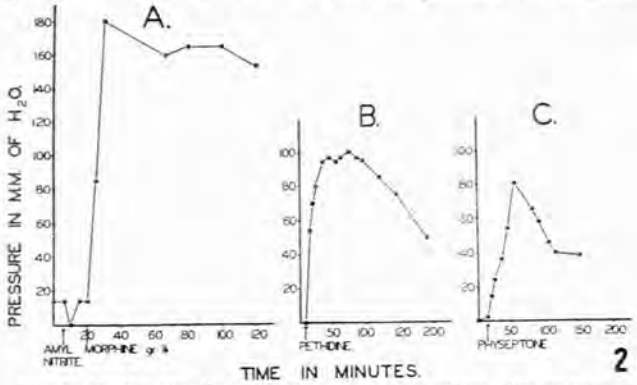

Fig. 2. Graphs showing the effects of (A) morphine, (B) pethidine and (C) physeptone on the intrabiliary pressure.

After the short-lived effect of the amyl nitrite had worn off the sphincter tone returned. Morphine, ¼ gr., was given intramuscularly and within 5 minutes the pressure started to rise, reaching a peak of 180 mm. of water after 15 minutes. This rise in pressure lasted about 2 hours. A similar rise in pressure was produced by pethidine and 'physeptone' (Graphs 2B and 2C).

Of all the available analgesics tested in this way (Table I) only 'avafortan' did not produce spasm of the sphincter of Oddi.

TABLE I. THE EFFECTS OF VARIOUS ANALGESICS ON THE SPHINCTER OF ODDI

Drug	*No. of administrations*	*Degree of spasm*			
		Nil	*Min.*	*Mod.*	*Marked*
Morphine	36	0	0	3	33
Omnopon	2	0	0	1	1
Pethidine	5	0	0	3	2
Physeptone	2	0	0	2	0
Avafortan	9	9	0	0	0
Baralgin	2	0	2	0	0

Min.=minimal, Mod.=moderate.

Combinations of various analgesics and antispasmodics were tested in a similar way.

The graphs in Fig. 3 show the effect of morphine combined with various antispasmodics on the intrabiliary pressure. Amyl nitrite produces immediate and complete relaxation of the spasm of the sphincter of Oddi caused by morphine (Fig. 3A). Unfortunately amyl nitrite cannot be inhaled for a long period, therefore its effect is short-lived and the pressure rises soon after the inhalation is stopped.

The combination of morphine and atropine is recommended by many[10-12] as the ideal analgesic in biliary pain on the assumption that atropine acts as an antispasmodic.[6,18] As can be seen in Fig. 3B, atropine does not prevent the marked spasm and increase in intrabiliary pressure produced by morphine. The use of atropine as a biliary antispasmodic therefore appears ill-founded.[19,20]

Intramuscular aminophylline (Fig. 3C) maintains partial relaxation of the sphincter of Oddi, after an injection of morphine, for approximately an hour. Thereafter the intra-

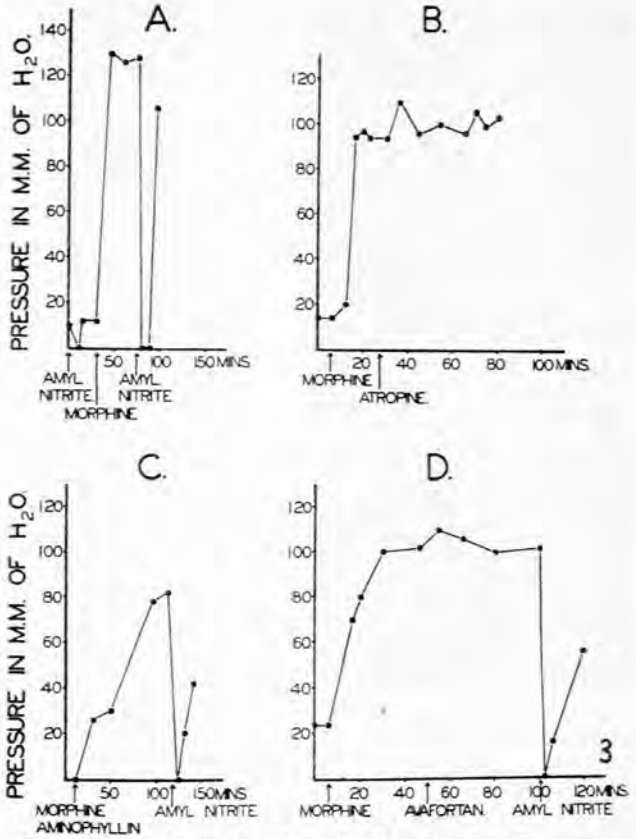

Fig. 3. Graphs showing the effects of (A) amyl nitrite, (B) atropine, (C) aminophylline and (D) avafortan on the intrabiliary pressure, following an injection of morphine.

biliary pressure rises. Amyl nitrite was given at the end of the experiments simply to ascertain that the apparatus was functioning properly. Intramuscular aminophylline has the disadvantage of being a painful injection.

Intramuscular avafortan (Fig. 3D) has no effect on the raised intrabiliary pressure produced by morphine. In some patients avafortan relaxes the tone of a normal sphincter of Oddi.[17]

None of the other antispasmodics tried in combination with morphine have any effect on the spasm of the sphincter of Oddi produced by the morphine (Table II). Therefore, at present avafortan — an analgesic that does not produce spasm

TABLE II. THE EFFECTS OF VARIOUS ANTISPASMODICS ON SPASM OF THE SPHINCTER OF ODDI PRODUCED BY MORPHINE

Drug	*No. of administrations*	*Degree of relaxation of spasm produced by morphine*			
		Nil	*Min.*	*Mod.*	*Marked*
Amyl nitrite	52	0	0	0	52
Aminophylline	5	1	1	3	0
Glycerine trinitrite	3	2	1	0	0
Atropine	6	6	0	0	0
Avafortan	6	5	1	0	0
Buscopan	3	2	1	0	0
Bentyl	4	3	0	0	1
Khellin	2	2	0	0	0
Papaverine	1	1	0	0	0
Priscol	2	2	0	0	0
Daptazole	3	3	0	0	0
Scopolamine	2	2	0	0	0
Ephedrine	2	2	0	0	0
Nalorphine	3	2	0	0	1

Min.=minimal, Mod.=moderate.

of the sphincter of Oddi — appears to be the best drug in the treatment of biliary colic due to a gallstone in the common bile duct.

The potency of avafortan is apparently equivalent to that of pethidine. Intramuscular avafortan has been tried in 3 cases of biliary colic caused by stones in the common bile duct with good results in 2 patients and an indifferent result in the third. Since the manufacturers advise that in cases of severe colic avafortan is more effective if given intravenously, it is possible that intravenous avafortan would have been more effective in our third patient.

EFFECT OF DRUGS ON THE GALLBLADDER

The effects of these drugs on the gallbladder were then investigated.

Morphine

Morphine is said to cause contraction of the gallbladder.[7,21] This conclusion was based on the following experiment:

A de Pezzer catheter or T-tube was inserted into the fundus of a gallbladder in a dog. The long limb of the T-tube was brought out through a stab wound in the abdominal wall and the abdomen closed. After the dog had recovered from the operation, a water manometer was attached to the catheter and the effect of morphine was tested with the dog at rest.

Fig 4 shows a graph of the pressure studies in this experiment. The resting pressure in this dog's gallbladder

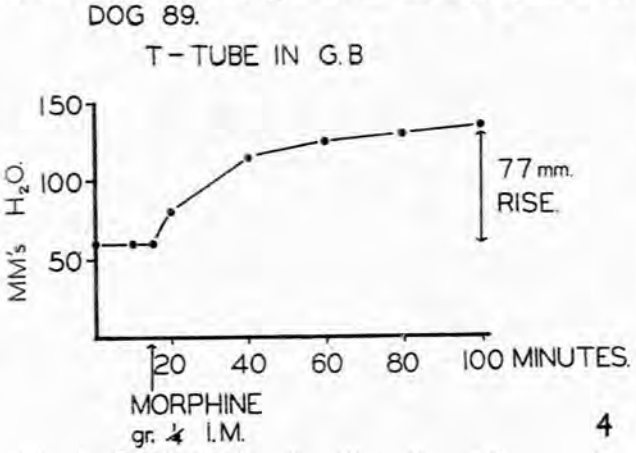

Fig. 4. Graph showing the effect of morphine on the intra-gallbladder pressure in a dog. (G.B.=gallbladder, I.M.=intramuscularly.)

was 60 mm. of water. Morphine, gr. ¼, was given intramuscularly. This resulted in a rise in intra-gallbladder pressure by 77 mm. of water. A similar rise in gallbladder pressure was obtained with pethidine.

There are 2 possible explanations for the rise in gallbladder pressure after the morphine injection (Fig. 5). Firstly, Macht[7] concluded that the rise in pressure was due to the contraction of the gallbladder itself. It is noteworthy that he did not ligate the cystic duct and did not carry the experiment further. A second possible explanation for the rise in pressure could be back pressure transmitted up the cystic duct from the raised intra-common-duct pressure produced by spasm of the sphincter of Oddi.

It was therefore felt that the experiment should be repeated after ligation of the cystic duct, but with the

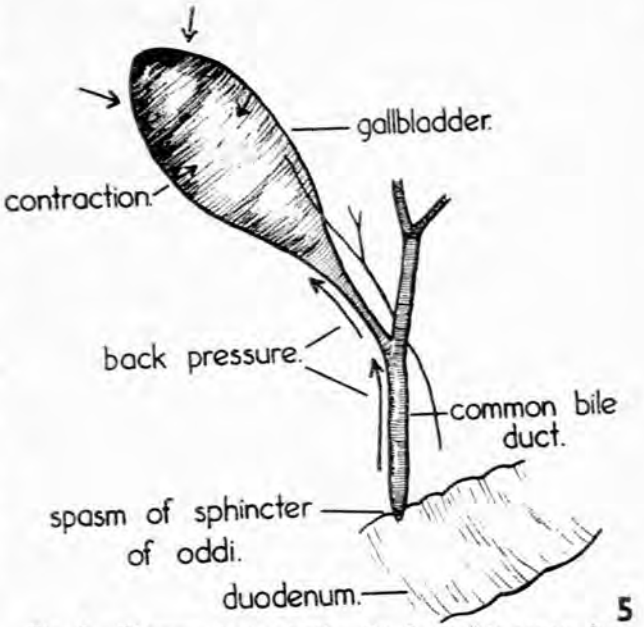

Fig. 5. Diagram demonstrating the 2 possible causes for a rise in the gallbladder pressure after an injection of morphine.

blood supply to the gallbladder intact. After ligation of the cystic duct morphine had no effect on the gallbladder pressure (Fig. 6A). In order to ascertain that the blood supply to the gallbladder was unimpaired after ligation of the cystic duct the dogs were given pancreozymin, a pancreatic hormone which contains cholecystokinin.[22] The

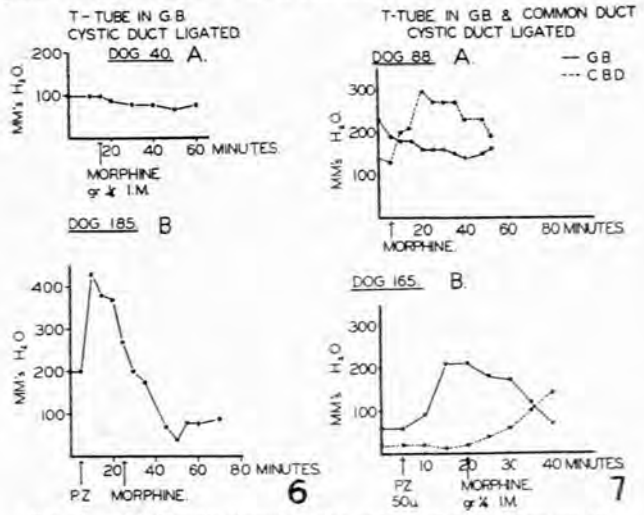

Fig. 6. (A) Graph showing the effect of morphine on the gallbladder of a dog after ligation of the cystic duct. (B) Graph showing the effects of pancreozymin and morphine on the gallbladder of a dog after ligation of the cystic duct. (G.B.=gallbladder, I.M.=intramuscularly, P.Z.=pancreozymin.)

Fig. 7. (A) Graph showing the effect of morphine on the gallbladder and the common-duct pressure following ligation of the cystic duct. (B) Graph showing the effects of pancreozymin and morphine on the gallbladder and the common-duct pressure following ligation of the cystic duct. (G.B.=gallbladder, CBD=common bile duct, PZ=pancreozymin, I.M.=intramuscularly.)

intravenous injection of pancreozymin (Fig. 6B) produced a short-lived but marked contraction of the gallbladder, lasting approximately 20 minutes.[23,24]

Here again there was no rise in gallbladder pressure after the injection of morphine. In fact, the pressure fell below the resting pressure, suggesting that the gallbladder may indeed have relaxed.

It remained to be shown that although there was no rise in pressure in the gallbladder after ligation of the cystic duct, there was indeed a simultaneous rise in common-bile-duct pressure. After ligation of the cystic duct, T-tubes were inserted into the gallbladder and into the common bile duct. Subsequently pressures were measured.

Following an injection of morphine (Fig. 7A) the pressure in the common bile duct rose to 140 mm. above that of the gallbladder pressure. The gallbladder pressure gradually fell after the morphine injection.

An attempt was then made to reproduce an attack of gallbladder colic in the experimental animal to observe the effect of morphine on the pressures in the biliary system in these circumstances.

A dog with T-tubes inserted into the gallbladder and common bile duct and whose cystic duct had been ligated, was given 50 units of pancreozymin, to produce acute gallbladder contraction. The graph in Fig. 7B shows that after the injection the pressure in the gallbladder rose steeply, whereas the common-duct pressure remained unchanged. At the height of the contraction ¼ gr. of morphine was given intramuscularly. The common-duct pressure rose steadily to above the gallbladder pressure, while the gallbladder pressure fell after the effect of the pancreozymin had worn off.

These experiments seemed to prove that morphine does not cause contraction of the gallbladder and perhaps even relaxes it, the rise in gallbladder pressure after morphine being due to back pressure up the cystic duct from the raised intra-common-duct pressure, caused by spasm of the sphincter of Oddi. It was thought possible that the back pressure in the cystic duct after the injection of morphine could disimpact a gallstone from the neck of the gallbladder and, with this in view, the following experiment was performed.

TABLE III. THE EFFECT OF MORPHINE ON THE HUMAN GALLBLADDER IN 6 CASES

Patient	*Effect of morphine on gallbladder*	*Effect of a fatty meal after morphine*	*Remarks*
1. L. B.	Increased distension	Increased distension	
2. M. J.	Slight contraction	No contraction	Patient vomited after morphine? Cause of contraction
3. S. G.	No contraction	No contraction	
4. L. P.	No contraction	No contraction	
5. J. B.	No contraction	No contraction	Gallbladder contracted following 2nd fatty meal 4 hours after morphine
6. F. de G.	Increased distension	Increased distension	

The gallbladder in a dog was mobilized from the fundus down and circumcised at the neck after the insertion of stay sutures. A close-fitting human gallstone was inserted into the neck of the gallbladder, making sure that it was not impacted and that it could be dislodged fairly easily (Fig. 8). The gallstone in the neck of the gallbladder was observed for 10 minutes under basal conditions.

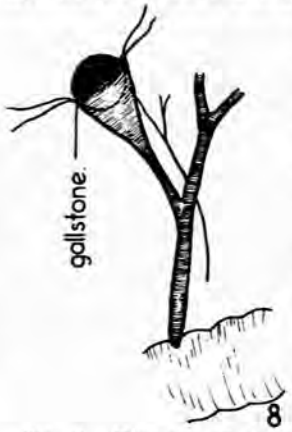

Fig. 8. Diagram of experiment in a dog showing a human gallstone inserted into the neck of the gallbladder.

The dog was then given ¼ gr. of morphine. Within 3 - 10 minutes, depending on the method of administration of the morphine, the stone was dislodged from the neck of the gallbladder.

This experiment was performed several times with the same result and it therefore seems reasonable to conclude that, given the correct conditions, morphine may dislodge a gallstone from the neck of the gallbladder in a dog.

In order to assess the value of the conclusions drawn from the above experiments performed on the gallbladders of dogs, it was necessary to determine whether the human and canine gallbladders react in the same way to drugs. This was investigated in the following way:

Six patients having routine cholecystograms, whose gallbladders had been filled adequately with dye, were given ⅛ - ¼ gr. of morphine intramuscularly. They were re-X-rayed from ½ to 2 hours after the morphine injection to observe the effect. The patients were then given fatty meals at varying intervals to see the effect of a stimulant on gallbladder contraction. Similar X-ray views were taken throughout the series.

Table III shows the effect of morphine on the gallbladder in the 6 patients. There was no contraction of the gallbladder after the morphine injection, except in patient 2 (M.J.). She vomited after the morphine was administered and this may have caused the gallbladder to contract and empty. Following morphine, the gallbladder failed to contract after a fatty meal in all cases.

In patient 5 (J.B.), the gallbladder had not altered in size ½ an hour after the injection of morphine. Similarly the gallbladder did not contract after the fatty meal. However, 4 hours after the morphine injection the fatty meal was repeated and on this occasion the gallbladder contracted, i.e. after the effect of the morphine had worn off.

In order to exclude delay of the fatty meal reaching the duodenum due to gastric stasis produced by morphine, a tube was passed into the duodenum in 3 cases and the fatty meal injected directly into the duodenum. Even under these circumstances the gallbladder did not contract.

From this it was concluded that morphine did not make the human gallbladder contract and appeared to inhibit the contraction normally produced by a fatty meal.

Atropine

It has been said that atropine causes the gallbladder to relax.[25] The effect of atropine on the human gallbladder

was tried on 4 patients who were having routine cholecystograms. Each patient was given $\frac{1}{100}$ gr. of atropine intramuscularly and re-X-rayed 15 minutes after the injection. This was followed by a fatty meal, and a further X-ray. In 3 cases the gallbladder decreased in size after atropine and in 1 case the gallbladder increased in size. In all 4 patients the gallbladder contracted in response to the fatty meal.

From these results it seems that atropine does not inhibit contraction of the gallbladder produced by a fatty meal and therefore is probably not of value as an antispasmodic in gallbladder pain.[26]

CONCLUSIONS

From these observations the following conclusions in regard to the treatment of biliary pain seem justifiable:

1. If the pain is due to a common duct stone, avafortan is the drug of choice. It is analgesic and does not produce spasm of the sphincter of Oddi. However, a more potent analgesic and antispasmodic drug would be preferable.

2. If the pain is due to a stone impacted in the neck of the gallbladder, morphine is the drug to be used. It is a powerful analgesic and does not cause contraction of the gallbladder. Indeed, it may even inhibit gallbladder contraction. Furthermore, due to contraction of the sphincter of Oddi, a rise in common-bile-duct pressure is caused which may be transmitted *via* the cystic duct and may result in disimpaction of the stone with complete remission of symptoms.

SUMMARY

1. The effects of various analgesics on the sphincter of Oddi, alone and in combination with various antispasmodics, are shown.

2. Of all the analgesics tested only avafortan does not produce spasm of the sphincter of Oddi.

3. The effect of morphine on the gallbladder is demonstrated.

4. Morphine does not cause the gallbladder to contract and perhaps even inhibits contraction. Furthermore, it was shown in dogs that spasm of the sphincter of Oddi produced by the morphine results in a rise in the common-duct pressure which may be transmitted up the cystic duct and dislodge a gallstone from the neck of the gallbladder.

5. It is suggested that in the treatment of biliary pain, if the pain is due to a common duct stone, avafortan is the drug of choice since it is an analgesic that does not produce spasm of the sphincter of Oddi. However, if the pain is due to a stone impacted in the neck of the gallbladder, morphine should be used.

A powerful analgesic which does not cause contraction of the gallbladder, morphine raises the common duct pressure, and this rise in pressure may be transmitted up the cystic duct to result in disimpaction of the stone with relief of symptoms.

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