ANALGESIA IN PANCREATITIS WITH SPECIAL REFERENCE TO THE EFFECT ON PRESSURE IN THE COMMON BILE-DUCT*

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The agonizing pain of acute pancreatitis requires a potent analgesic for its relief and in the past morphine was recommended. That morphine causes spasm of the sphincter of Oddi has been shown, amongst others, by Prof. J. H. Louw,[1] Butsch *et al.*[2] and Nossel and Efron.[3] This fact is significant because, firstly, one of the more popular current theories of the aetiology of acute pancreatitis is that of biliary reflux up the pancreatic duct as a result of spasm of the sphincter of Oddi.[4] Secondly, it has been shown that one of the causes of pain in pancreatitis is the raised intraductal pressure due to spasm of the sphincter of Oddi.[5] Whether one favours the biliary-reflux theory or not, Nossel and Efron[3] showed that morphine may cause a rise of serum amylase in a normal person (2 cases out of 43) and that the probable mechanism of this rise was spasm of the sphincter of Oddi.

This investigation was carried out in an attempt to find a suitable analgesic agent for the relief of pain in acute pancreatitis, with special reference to possible side-effects on pressure in the common bile-duct.

Material and Methods

The investigations were carried out on patients who had undergone cholecystectomy for gall-bladder disease and in whom T-tube drains had been left in the common bile-duc after exploration. None of these patients had any history suggestive of pancreatitis and in all of them the short limb of the T-tube was at least $\frac{1}{2}$ inch away from the ampulla of Vater. All the cases were investigated approximately 10 days after the operation after patency of the common bile-duct was demonstrated by cholangiography.

Apparatus Used

The pressure apparatus (Fig. 1) consists of a water manometer which is connected (1) to the T-tube emerging from the abdominal wall and (2) by means of a Y-tube to a vacolitre of normal saline, used (*a*) to fill the system and (*b*) to increase the ductal pressure, if necessary. In this way the pressure required to overcome the sphincter tone is determined.

The manometer and tubing are filled with saline by the drip and connected to the T-tube. The drip is then clamped off. Throughout the experiment the patient lies at ease and restful in bed. Once the level in the manometer is constant (there is a variation of the meniscus with respiration of ± 1 cm.), a reading is taken. The patient is now given amyl nitrite to inhale, which completely relaxes the sphincter of Oddi. The pressure falls from 8 to 15 mm. of water and a reading is taken again. The latter reading is regarded as the zero line. After a few minutes the pressure rises again to approximately the level before the amyl nitrite was inhaled. The difference between this pressure and the zero level is called the 'resting intrabiliary pressure' which is thought to

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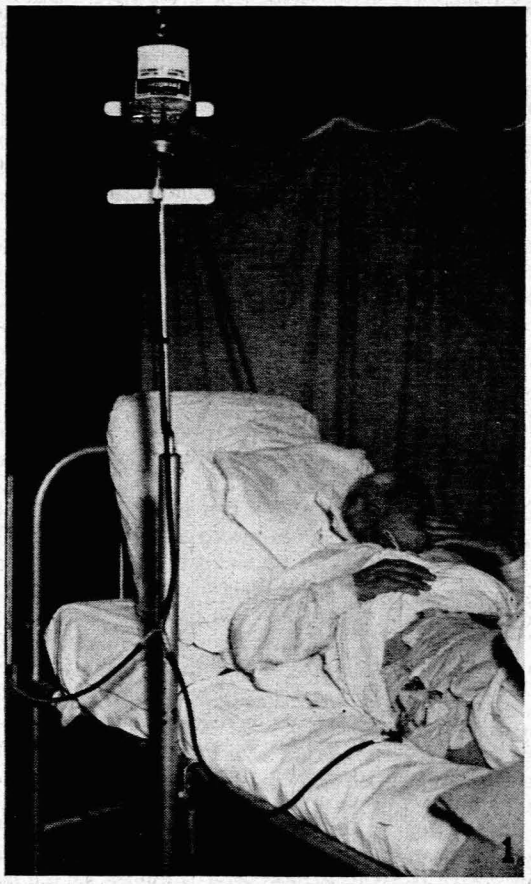


Fig. 1. The apparatus used for measuring intrabiliary pressure.

be due to the normal tone of the sphincter of Oddi. The patient is then given the drug to be tested and the readings recorded.

Intrabiliary Pressures

The graph in Fig. 2 shows the effect of morphine on the sphincter of Oddi. The resting intrabiliary pressure was

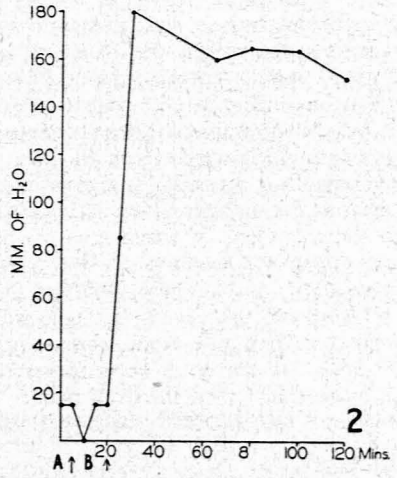


Fig. 2. Graph showing the effect of morphine on the intrabiliary pressure. A=amyl nitrate. B=morphine gr. $\frac{1}{6}$.

15 mm. of water. Morphine, 1/6 gr., was injected intramuscularly. The pressure started to rise within about 5 minutes and reached a peak of 180 mm. after 15 minutes. The rise in pressure lasted about 2 hours.

The next experiment was an attempt to show that when a rise in serum amylase is produced by morphine, it is due to spasm of the sphincter of Oddi. One of the patients, in whom it was found that morphine produced an abnormally raised serum amylase, was explored for stone in the common bile-duct and a T-tube left in her common duct. Post-operative intrabiliary pressures were measured at frequent intervals and serum-amylase levels were determined $\frac{1}{2}$ hour before and $2\frac{1}{2}$ hours and $3\frac{1}{2}$ hours after an injection of morphine.

Two days later the test was repeated with the drip opened and the pressure of the fluid in the bile duct raised to between 350 and 450 mm. of water, till the saline flowed steadily through into the duodenum at a rate of 60 drops per minute—in this way maintaining patency of the sphincter of Oddi. The serum-amylase values were again determined before and after an injection of morphine. In Table I the results are shown of the simultaneous studies on bile-duct pressures

TABLE I. THE RESULTS OF BILE-DUCT PRESSURES AND SERUM-AMYLASE VALUES

Elevation of Bile-Duct Pressure in mm. of water		*Duration of Elevation of Pressure (minutes)*	*Serum Amylase*		
			Premed	*2½ hrs.*	*3½ hrs.*
1	140–160	180	8μ	56μ	56μ
2	345–455 (Perfusion pressure)	150	8μ	8μ	8μ
3	140–160	170	8μ	52μ	46μ

Morphine $\frac{1}{6}$ gr. given hypodermically

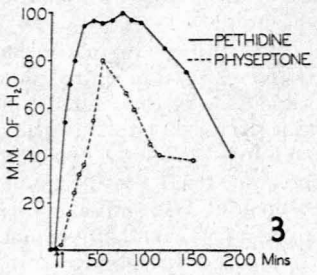
and serum-amylase values (with and without perfusion of the common bile-duct) after an injection of morphine. (Serum-amylase values were determined according to Wohlgemuth's method. Normal values for our laboratory are 3-10 units per c.c.)

After an injection of morphine, the rise in serum amylase was abolished by maintaining complete patency of the sphincter of Oddi. From this it appeared that a rise in the serum amylase produced by morphine was probably due to its mechanical action on the sphincter of Oddi and not to any effect on the secretory activity of the gland. It was therefore apparent that morphine, or any drug that causes spasm of the sphincter of Oddi, was unsuitable as an analgesic in the treatment of acute pancreatitis, and that the ideal drug, or combination of drugs, should be a potent analgesic as well as an antispasmodic of the sphincter of Oddi. The purpose of this work was to find such a drug. Many substances and combinations were tried, some of which will be dealt with here.

Analgesic Drugs Used

1. *The opiates* all behaved in the same fashion as morphine. Twelve experiments were done with morphine—the average rise in pressure was 110 mm. of water. Omnopon was used in one patient. The pressure started rising after 5 minutes and reached a peak of 80 mm. of water after 50 minutes.

2. *Pethidine and physeptone*, which are said to have the central analgesic effect of morphine without the spasmodic effect on the sphincter of Oddi, were also tried. Both these drugs are less potent analgesics than morphine and their effect on the sphincter of Oddi and on intrabiliary pressure is indicated in Fig. 3. Both pethidine and physeptone cause



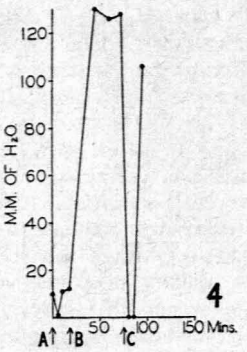


Fig. 3. Graph showing the effect of pethidine and physeptone on intrabiliary pressure.
Fig. 4. Graph showing the effect of amyl nitrite on spasm of the sphincter of Oddi produced by morphine. A=amyl nitrite. B=morphine. C=amyl nitrite.

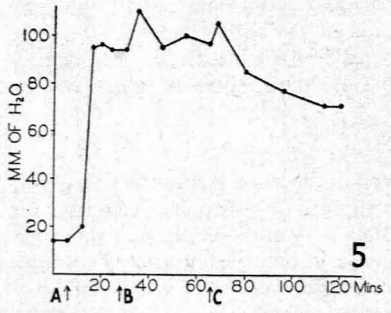
a rise in intrabiliary pressure. With pethidine the intrabiliary pressure rose to a maximum of about 100 mm. of water in 20 minutes and started to fall after 95 minutes. Radiologists are aware that pethidine causes spasm of the sphincter of Oddi and give intravenous pethidine to produce this spasm in doing biligrafin studies. Physeptone, a poorer analgesic, produces a slower rise in intrabiliary pressure, which starts to fall after 1 hour.

Combinations of Analgesics and Antispasmodics

(i) *Morphine and amyl nitrite* (Fig. 4). Amyl nitrite produces immediate and complete relaxation of the spasm (of the sphincter of Oddi) produced by morphine. This relaxation is short-lived and the pressure rises once the inhalations are stopped. Unfortunately amyl nitrite cannot be inhaled for a long period of time because of unpleasant side-effects.

(ii) *Morphine and glycerine trinitrate.* Glycerine trinitrate is not as effective an antispasmodic as amyl nitrite and, unless a large dose is used, one does not get much relaxation of the sphincter of Oddi.

(iii) *Morphine and atropine.* This combination is recommended by many on the assumption that the atropine acts as an antispasmodic. Atropine does not appear to have any effect on the sphincter of Oddi (Fig. 5). It certainly does not overcome or prevent the marked spasm and increase in intrabiliary pressure produced by morphine. The use of atropine as a biliary antispasmodic therefore appears ill-founded.



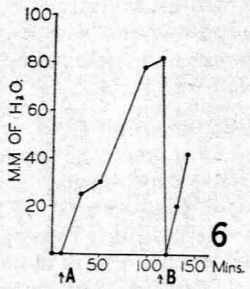


Fig. 5. Graph showing the effect of atropine and aminophyllin on intrabiliary pressure following an injection of morphine. A=morphine. B=atropine. C=aminophyllin.
Fig. 6. Graph showing effect of an injection of morphine and aminophyllin given simultaneously on intrabiliary pressure. A=morphine and aminophyllin. B=amyl nitrite.

However, there is place for atropine, or related substances such as probanthine, in the treatment of acute pancreatitis, *viz.* as vagal secretory inhibitors.

(iv) *Morphine and aminophyllin.* Intramuscular aminophyllin was used in this experiment. Aminophyllin appears to maintain partial relaxation of the sphincter after an injection of morphine for ± 1 hour, after which the intrabiliary pressure rises (Fig. 6). The disadvantage of intramuscular aminophyllin is that it is a painful injection.

The other combinations of drugs tried were as follows: Morphine and khellin, morphine and papaverine, morphine and priscol, morphine and daptazole, morphine and scopolamine and morphine and ephedrine. All these antispasmodics were unable to overcome the increase in intrabiliary pressure produced by morphine. The combination of morphine and nalorphine was also tried (Fig. 7). The nalorphine was injected 40 minutes after the injection of morphine. The nalorphine relaxes the spasm produced by morphine, but unfortunately it neutralizes the analgesic effect of morphine as well.

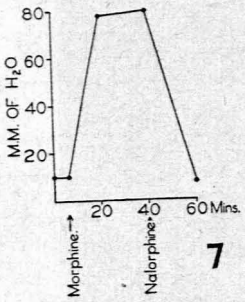


Fig. 7. Graph showing the effect of nalorphine on intrabiliary pressure following an injection of morphine.

The effects of amyl nitrite, glycerine trinitrate, aminophyllin and atropine were tried on the spasm of the sphincter of Oddi produced by pethidine and physeptone. The results were very similar to that obtained with morphine.

AVAFORTAN

At this stage a new drug, avafortan, was received for clinical trial. A few facts about avafortan, as supplied by the manufacturers, are relevant: Avafortan is free from alkaloids and consists of 2 components: avapyrazone and pyrazolone. Its chemical formula is as follows:

(1) Iso amyl ∝[N-(β diethylaminoethyl)]-amino-phyl acetate-bis-phenyldimethyl-pyrazolone-methyl-amino-methane-sulphonate (avapyrazone).
(2) Sodium-phenyl-dimethyl-pyrazolone-methylamino-methane-sulphonate (pyrazolone).

(i) The avapyrazone has an anticholinergic action—it relieves spasm of smooth muscle in the bile ducts, urinary tract, bronchi and blood vessels (coronary blood flow is markedly increased). It is interesting to note that it relieves bronchospasm, which may be a prominent feature of acute pancreatitis. We had such a case in the wards recently.

(ii) The pyrazolone is a central analgesic and it is stated that it also has an anti-inflammatory action, which may be important in the treatment of spasm due to inflammation.

Toxicity and tolerance. Avafortan is well tolerated with a wide margin of safety. Unlike the opiates and their synthetic substitutes it is stated that avafortan will not mask the acute abdomen. I have not come across any untoward effects of the drug. It can be given intramuscularly, intravenously and by mouth. I used the drug mainly intramuscularly (4-5 c.c.) and found this to be a painless injection.

Tests with Avafortan

Avafortan was given to a large number of patients who had been on various analgesics for extensive carcinoma,

Buerger's disease, etc. and it was concluded that 4 c.c. of avafortan given intramuscularly was a slightly less potent analgesic than 100 mg. of pethidine. The analgesic and antispasmodic effects were determined in numerous cases of renal colic in the hospital. The results were excellent.

The effect of avafortan on the sphincter of Oddi and on intrabiliary pressure was tested on a male patient who had undergone cholecystectomy and exploration of the common

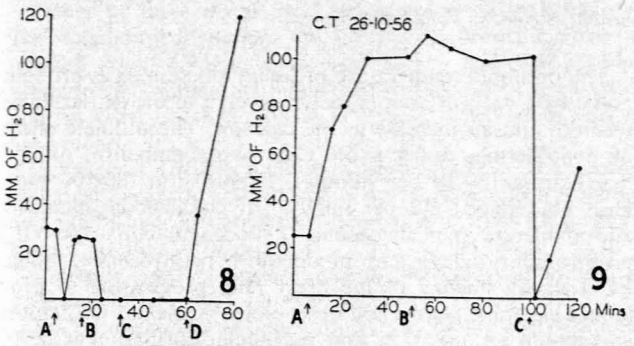


Fig. 8. Graph showing the effect of avafortan on resting intrabiliary pressure. A=amyl nitrite. B=avafortan. C=amyl nitrite. D=morphine.
Fig. 9. Graph showing the effect of avafortan on intrabiliary pressure after an injection of morphine. A=morphine. B=avafortan. C=amyl nitrite.

bile-duct (Fig. 8). The resting intrabiliary pressure was 30 mm. The patient was given amyl nitrite to inhale and the pressure fell to zero; 5 minutes later the pressure rose to 25 mm. of water. The patient was given 4 c.c. of avafortan intramuscularly and the pressure fell to zero after about 10 minutes. Five minutes later the patient was again given amyl nitrite to inhale and the pressure remained at zero. After 1 hour the patient was given 1/6 gr. of morphine intramuscularly. The pressure rose to 120 mm. of water after 20 minutes.

In another patient who was given avafortan there was no effect on the intrabiliary pressure. One hour later $\frac{1}{4}$ gr. of morphine was given and after 10 minutes the pressure started rising.

In a 3rd test (Fig. 9) the patient was given $\frac{1}{4}$ gr. of morphine intramuscularly. The pressure rose in the manometer to 100 mm. after 30 minutes. After a further $\frac{1}{4}$ hour, 4 c.c. of avafortan was given intramuscularly with no effect on the pressure. One hour after the injection of the avafortan the pressure was still at 100 mm. of water. At this stage the patient inhaled amyl nitrite. The pressure dropped to zero after 3 minutes. Ten minutes after the inhalation of amyl nitrite the pressure started rising again and went up to 50 mm. of water.

From these tests it was concluded that avafortan did not cause spasm of the sphincter of Oddi, perhaps had a slight antispasmodic effect on the sphincter, but was unable to release the spasm of the sphincter produced by morphine.

Clinical Trials with Avafortan

Clinically avafortan has been used in 19 cases of acute pancreatitis. In 16 cases the pain was relieved and in the other 3 partial relief was obtained. In no case was the pain aggravated. In 2 cases of acute cholecystitis, one patient obtained complete relief and the other had no relief. In 2 patients with biliary colic 1 case had relief after avafortan with the first attack but not subsequently. The other patient had no relief of pain. Perhaps all the patients who were unrelieved of their pain should have had intravenous avafortan as recommended.

A further observation was recently made with avafortan tablets. In a European female aged 79 a routine post-operative cholangiogram was made on the 10th day after an exploration of the common bile-duct for stone. The patient was symptomless. On screening, marked spasm of the sphincter of Oddi was found. It took a fair amount of pressure to overcome the spasm. The lipiodol flowed through into the duodenum after 3 minutes. The next day the intrabiliary pressure was measured (Fig. 10). The resting pressure was 20 mm. water. After amyl-nitrite inhalation the pressure fell to zero. Five minutes later the pressure rose to 15 mm. water. One tablet of avafortan was given and 2 hours later the pressure was zero; 4 hours later it was still zero. At this stage the cholangiogram was repeated. On this occasion much less pressure was required to inject the dye, which appeared in the duodenum after 15 seconds.

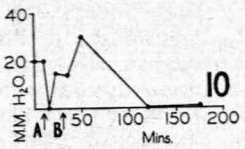


Fig. 10. Graph showing the effect of an avafortan tablet on intrabiliary pressure in a patient with spasm of the sphincter of Oddi. A=amyl nitrite. B=avafortan.

DISCUSSION

The above results raise interesting possibilities.

Firstly, if chronic relapsing pancreatitis is due to biliary reflux as a result of spasm of the sphincter of Oddi, should not the treatment of this condition be medical and sphincterotomy be replaced by a suitable antispasmodic? I have tried avafortan on one such case, who has done well. *Secondly*, avafortan may be the answer to so-called biliary dyskinesia (which is said to be due to spasm of the sphincter of Oddi).

It would appear that we have no ideal drug which simultaneously is a potent analgesic and an antispasmodic of the sphincter of Oddi for use in the treatment of acute pancreatitis. The disadvantages of the opiates and their derivatives, both alone and in combination with various antispasmodics, have been shown.

It appears that avafortan, although not the most potent analgesic available, does not produce spasm of the sphincter of Oddi and thus is the drug of choice at present.

We must search for a drug which will be an analgesic with a more powerful antispasmodic effect on the sphincter of Oddi. Such a drug will possibly replace the operation of sphincterotomy in the treatment of chronic relapsing pancreatitis and biliary dyskinesia.

SUMMARY

1. The effect of various analgesics alone and in combination with various antispasmodics on common-bile-duct pressure has been shown.

2. The results of a clinical trial of avafortan as an analgesic and antispasmodic are analysed.

3. The need for a more powerful analgesic and antispasmodic of the sphincter of Oddi is indicated, with particular reference to the treatment of pain in acute pancreatitis.

4. It is postulated that such a drug may be of value in the

treatment of cases of biliary dyskinesia and in chronic relapsing pancreatitis due to spasm of the sphincter of Oddi.

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