Action of various new analgesic drugs on the human common bile duct

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EDITORIAL COMMENT There is experimental evidence from the studies of these authors that phenazocine (Narphen) might be a particularly suitable analgesic for the treatment of biliary pain.

The pain of patients suffering from biliary tract disease is usually treated by administering morphine or pethidine, with or without an antispasmodic drug such as aminophylline; but both these analgesics cause spasm of the sphincters controlling the flow of bile into the duodenum. In 1936, Butsch, McGowan, and Walters reported typical biliary colic occurring after giving morphine to patients following cholecystectomy and T-tube drainage of the common duct, and were able to correlate this pain with a rise in common bile duct pressure. Bergh and Layne (1940) attributed post-morphine pain to spasm of the sphincter of Oddi.

More recently, raised serum amylase and serum lipase levels have been demonstrated in normal subjects after giving morphine and secretin (Myhre, Nesbitt, and Hurly, 1949; Burke, Plummer, and Bradford, 1950). Radiographic studies have conclusively shown spasm of the common bile duct sphincter after giving morphine (Caroli, Porcher, Pequignot, and Delattre, 1960).

Pethidine can also be shown to cause spasm of the sphincter and raise the bile duct pressure although to a less but still significant extent than morphine (Figs. 1 and 2).

The immediate cause of biliary pain is thought to be either increased duct pressure or ischaemia induced by sphincter muscle spasm or a combination of both factors. Often these two conditions will be aggravated by local inflammation or irritation such as that caused by a stone passing down the duct or arrested in the lower portion of the duct. It is clearly illogical to treat biliary pain with drugs which cause sphincter spasm and increased bile duct pressure; but because of the central analgesic and sedative effects of morphine and pethidine it is justified to use these drugs when no better is available.

During recent years several powerful new analgesic drugs have been made available, but little work has been reported on their action on the biliary tract. Efron (1958) reported that Avafortan caused no spasm of the biliary sphincter, and recommended this drug for treating pain of common bile duct origin. Unfortunately, the active principle in Avafortan is amidopyrine; on occasion this drug causes agranulocytosis and its use is no longer justified. Boulter (1961) investigated the effect of levorphanol (Dromoran) on the flow rate of saline through the human common bile duct and concluded that this drug caused spasm of the sphincter as marked as that caused by morphine. Robelet, Bizard-Gregoire, and Bizard (1965) reported the effect of dextromoramide (Palfium) on the perfused common bile duct of the guinea-pig. Intravenous injection of this drug stopped the perfusion, indicating spasm of the sphincter. Crema, Benzi, Frigo, and Berté (1965), after perfusion experiments on the bile ducts of dogs and cats, concluded that morphine, meperidine, levorphanol, methadone, and dextromoramide injected intravenously were strongly active on the terminal bile duct, reducing flow through it.

This paper reports the effects of pressure in the human common bile duct of five new analgesic drugs administered parenterally.

METHOD

Investigations were made with the willing cooperation of patients after cholecystectomy and during T-tube drainage of the common bile duct.

Pressure changes in the common bile duct were transmitted through a T-tube connected to a saline-filled glass U-tube manometer. Fluctuations in pressure were recorded by an ink-writing pen attached to a float. Zero reference was obtained for each investigation by adjusting the 5 cm. mark of the manometer to the level at which the T-tube entered the skin. This arbitrary reference point was chosen for its convenience in recognition and because the important measurement was of changes in common bile duct pressure rather than absolute values. The apparatus was primed with sterile normal saline at the
beginning of the recording but no attempt was made to perfuse the duct. Any pressure rise was thus dependent on the continued secretion of bile by the liver, and it was assumed that this occurred at a constant rate during the investigation.

No investigation was carried out less than 10 days after operation. Fluctuation in the rate of bile secretion was minimized by fasting of the patient although drinks of water were allowed.

In most of the patients the common bile duct had been explored by passing a sound downwards through the sphincter into the duodenum. In some of these patients a duodenotomy had then been carried out and the mucosa at the tip of the ampulla of Vater had been incised. In no case, however, was a sphincterotomy performed which would extend as high as the choledochal sphincter.

**ASSESSMENT OF PRESSURE CHANGES**

The pressure changes after injecting morphine and pethidine are well recognized and these were used as a basis for comparison of the effects of the new analgesics. Any rise in pressure was classified under one of four headings.

- **MARKED** pressure rise, 10 cm. or more, usually occurs after giving morphine.
- **MODERATE** pressure rise, 5-10 cm., usually occurs after giving pethidine.
- **MINIMAL** pressure rise, less than 5 cm. or a sharp spike on the tracing lasting for less than five minutes, may be due to small positional changes of the patient, or to coughing or straining.
- **NIL**; no change in pressure.

**RESULTS**

Morphine (10 mg. i.m.) was administered on four occasions and a marked rise in pressure was recorded each time (Fig. 1).

Pethidine (100 mg. i.m.) was given on four occasions and a moderate rise in pressure was recorded each time (Fig. 2).

**FIG. 1.** Typical tracing showing marked rise in common bile duct pressure after giving morphine, 10 mg. intramuscularly.

**FIG. 2.** Tracing of pressure in common bile duct showing a moderate rise after giving pethidine, 100 mg. intramuscularly.
TABLE I
DETAILS OF THE FIVE DRUGS TESTED

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proprietary Name</th>
<th>Approved Name</th>
<th>Analgesic Strength</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dromoran</td>
<td>Levorphanol</td>
<td>2 mg. i.m. comparable with 10 mg. morphine i.m.</td>
<td>Oral 3</td>
<td></td>
</tr>
<tr>
<td>Palium</td>
<td>Dextromoramide</td>
<td>5 mg. i.m. comparable with 10 mg. morphine i.m.</td>
<td>Intramuscular 4</td>
<td></td>
</tr>
<tr>
<td>Doloxene</td>
<td>Dextropropoxyphene Hydrochloride</td>
<td>Comparable with codeine</td>
<td>Intravenous 2</td>
<td></td>
</tr>
<tr>
<td>Operidine</td>
<td>Phenoperidine</td>
<td>2 mg. i.m. comparable with 10 mg. morphine i.m.</td>
<td>Oral 9</td>
<td></td>
</tr>
<tr>
<td>Narphen</td>
<td>Phenazocine</td>
<td>2 mg. i.m. stronger than 15 mg. morphine i.m.</td>
<td>Intramuscular 2</td>
<td></td>
</tr>
</tbody>
</table>

TABLE II
EFFECTS OF FIVE DRUGS ON BILIARY PRESSURE

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Investigations</th>
<th>Effect on Pressure in Common Bile Duct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nil</td>
<td>Minimal</td>
</tr>
<tr>
<td>Morphine</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pethidine</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Dromoran</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Palium</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Doloxene</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Phenoperidine</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Narphen</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

occasions also and a moderate pressure rise was recorded on each occasion (Fig. 2).

The five new analgesics which were investigated are listed in Table I, and Table II summarizes the results.

LEVORPHANOL (DROMORAN) This strong analgesic was given as a 2 mg. intramuscular injection. It was administered on three occasions to different patients. On all three occasions, the pressure rose, twice to a marked extent and once to a moderate extent.

DEXTROMORAMIDE (PALFIUM) This strong analgesic was given four times by intramuscular injection of 5 mg. On two occasions a moderate rise in pressure occurred and on two occasions a minimal rise in pressure occurred.

DEXTROPROPOXYPHENE HYDROCHLORIDE (DOLOXENE) This relatively weak analgesic is marketed in tablet form only in the United Kingdom. However, the manufacturers provided 100 mg. ampoules for intramuscular injection and this drug was administered orally twice and by injection three times. On no occasion was any change in pressure recorded.

PHENOPERIDINE (OPERIDINE: DIPHENYL PROPYLAMINE) The degree of analgesia obtained with this drug depends upon the dose. Two mg. intramuscularly produces a strong analgesic effect. Phenoperidine was given intramuscularly nine times in this dosage and 1 mg. was given intravenously twice. On eight occasions, no pressure rise was recorded. Three times, including both those occasions when the drug was given by intravenous injection, a minimal pressure rise occurred.

PHENAZOCINE (NARPHEN) This very strong analgesic was given six times as a 2 mg. intramuscular injection. On four occasions, no pressure rise was recorded, but two injections were followed by minimal rises in pressure (Fig. 3).
DISCUSSION

The structure of the sphincter of Oddi at the lower end of the common bile duct has been fully described by Boyden (1957). He clearly demonstrated that the sphincter of Oddi is a composite structure. The ampullary or papillary sphincter surrounds the tip of the ampulla of Vater and the common bile duct and pancreatic duct each have a separate sphincter. The biliary sphincter consists of two parts, the superior and inferior bile duct or choledochal sphincters, and the flow of bile into the duodenum is mainly controlled by these muscles.

The duodenal musculature may also have some constricting action around the ampulla of Vater and certainly raised pressure in the duodenal lumen could cause obstruction to the flow of bile from the common bile duct and thus cause a rise in bile duct pressure (Kock, Kewenter, and Jacobsson, 1964). However, the extent to which these separate factors influence the bile duct pressure is still not clear and our investigations did not differentiate between the possible causes of the obstruction to bile flow. It would seem, however, that the most important cause of raised pressure in the bile duct after giving analgesic drugs is contraction of the choledochal sphincter.

Both levorphanol (Dromoran) and dextromoramide (Palfium) produced marked or moderate rises in pressure in the common bile duct after doses adequate to give useful analgesia. They show, therefore, no advantage over morphine or pethidine.

Dextropropoxyphene hydrochloride (Doloxene) has no apparent effect on common bile duct pressure and so presumably does not cause spasm of the biliary sphincters. It is, however, a comparatively weak analgesic, being more comparable with codeine than with morphine or pethidine (Gruber, 1957). Although it has been passed by the Dunlop Committee for intramuscular injection, it is not generally available in the United Kingdom in this form though it has been extensively used in tablet form.

Dextropropoxyphene hydrochloride (Doloxene) is unlikely to be of value in treating the severe pain associated with biliary colic and pancreatitis. We have, however, used it with success on two occasions in patients with chronic abdominal pain apparently due to secondary deposits in the liver arising from cancer of the large bowel. An added advantage is that it does not cause constipation.

Phenoperidine (Operidine) caused no rise in biliary pressure after intramuscular injection and only a minimal rise after intravenous injection. This drug is said to be a strong but short-acting analgesic. If given in slightly larger doses, it will depress respiration to a dangerous extent.

Phenazocine (Narphen) is a new potent narcotic analgesic which does not cause a rise in biliary pressure. This drug is less likely to cause respiratory depression, hypotension, or nausea than an equally potent dose of morphine, and tolerance develops more slowly. The effects of the drug are reversed by Nallorphone (Di Pillo, Younger, Scarpa, and Edson, 1960). It has also been demonstrated that phenazocine, unlike morphine, has little or no broncho-constrictor effect. Our results suggest that phenazocine also differs from morphine in having no effect on the biliary sphincters. Phenazocine is, therefore, on the basis of these investigations more suitable for treating pain of biliary origin than is morphine or pethidine.

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REFERENCES


