BILE SALTS AND NEUROMUSCULAR BLOCKING AGENTS

P. WESTRA, M. C. HOUWERTJES, H. WESSELING AND D. K. F. MEIJER

SUMMARY

The influence of the primary bile salts taurocholate and chenodeoxycholate on the neuromuscular blockade of the non-depolarizing drugs Org 6368, pancuronium, Org NC 45 and hexafluorenium was studied in cats. An increase in the effects of these agents, all possessing widely varying molecular structures, was found following administration of the bile salts. The bile salt concentrations in plasma were similar to those obtained after 9–10 days of extrahepatic cholestasis in cats. The effect of Org NC 45, a new monoquaternary analogue of pancuronium, was increased more than that of pancuronium. This increase in effect is probably a result of inhibition of the hepatic uptake of the neuromuscular blocking drugs. The neuromuscular blocking effect of gallamine was not influenced significantly by the administration of bile salts.

The liver stores and, to a lesser extent, excretes quaternary ammonium neuromuscular blocking agents such as tubocurarine (Cohen, Brewer and Smith, 1967; Meijer and Scaf, 1968; Vonk Scholtens et al., 1978; Meijer et al., 1979), hexafluorenium (Meijer, Vermeer and Kwant, 1971), pancuronium (Agoston, Kersten and Meijer, 1973; Agoston et al., 1973; Buzello, 1975) and Org 6368 (Agoston et al., 1977). However, the hepatic elimination of gallamine, another (tris)-quaternary agent, is negligible in man (Agoston et al., 1978), dog (Feldman, Cohen and Golling, 1969) and cat (Westra et al., 1980).

Studies in the cat by Agoston and colleagues (1977) revealed that, after 3 min, 9% of the total dose of pancuronium was present in the liver, compared with 41% for Org 6368. The liver is important in the removal of Org NC 45 from the blood stream, since temporary or permanent exclusion of the liver from the circulation has been shown to produce a significant increase in its duration of action (Durant, Houwertjes and Agoston, 1979). Although renal excretion of pancuronium is the main route of elimination in man (Agoston et al., 1973; Buzello, 1975), a considerable prolongation of neuromuscular blockade was reported by Somogyi, Shanks and Triggs (1977) in patients with extrahepatic cholestasis.

Recently we found a decrease in the plasma clearance and a prolongation of neuromuscular blockade with Org 6368 and pancuronium in cats with experimental cholestasis, while gallamine showed normal kinetics (Westra et al., 1980). Likewise, a prolongation of the duration of action of Org 6368 was obtained in the cat during (portal) infusion of the semi-synthetic bile salt dehydrocholate (Vonk et al., 1979) and it was suggested that the bile salt caused an inhibition of uptake of the neuromuscular blocker into the liver. Therefore, it is conceivable that pathologically increased concentrations of naturally occurring bile salts in extrahepatic cholestasis are, at least partially, responsible for the prolonged duration of action of neuromuscular blocking drugs by interfering with the hepatic uptake and subsequent biliary excretion of the drugs.

The aim of this study was to determine if infusion of the primary bile salts taurocholate and chenodeoxycholate decreased the plasma clearance and hepatic uptake of Org 6368, pancuronium, Org NC 45 and hexafluorenium and consequently prolonged their durations of action.

METHODS

Animal experiments

All experiments were carried out in adult cats, 2–5 kg body weight, of either sex, under sodium pentobarbitone anaesthesia (Nembutal, Abbott; 40 mg kg$^{-1}$ i.p., and maintenance doses of...
After orotracheal intubation, artificial ventilation of the lung with air through a cuffed Magill tube (5.5 mm) was maintained with a Braun respirator type 1955, set at a rate of 30 b.p.m. and a tidal volume of 10 ml kg\(^{-1}\). The e.c.g. (E.C.G.-Pulse Monitor, MS-35; Electrodyn Inc., U.S.A.), expired carbon dioxide concentration (capnograph, E. Jaeger, Wuerzburg, W. Germany) and mean arterial pressure (Statham P23D6 transducer; KWS 3085 HSE Elektro-Manometer) were monitored continuously. Mean arterial pressure was not less than 100 mm Hg in any experiment. Body temperature was kept constant at 36–38 °C by heating the operating table. Rectal temperature was measured with a thermistor (Elektrolaboriet, Copenhagen). To replace fluid loss, an aqueous solution of 2.5% glucose and 0.45% saline was infused through a polythene cannula in the external jugular vein. Neuromuscular studies (isometric twitch tension) were performed on the tibialis anterior muscle which was stimulated through the common peroneal nerve with supra-maximal square-wave pulses of 0.2 ms duration at a frequency of 0.1 Hz. The stimulus was supplied by a Grass S88 stimulator and a SIU5 stimulus isolation unit. The tendon of the tibialis anterior muscle was connected to a load cell (UL4-20, Statham), attached to a force-displacement transducer (UC3 Gold Cell, Statham), mounted securely on a Braun-Schuster myograph. The signal was amplified by a Hottinger-Baldwin amplifier (Messtechnik, Darmstadt) and muscle contractions were recorded continuously on a MFE two-channel polygraph (d.c. to 40 Hz, full scale). Following the administration i.v. of heparin 2000 i.u., a silicon catheter was placed in the hepatic portal vein to permit the administration of drugs into the portal system. After approximately 3 h another maintenance dose of heparin 1000 i.u. was given i.v. Org6368 100 μg kg\(^{-1}\), pancuronium 20–25 μg kg\(^{-1}\), Org NC 45 35–45 μg kg\(^{-1}\), hexafluorenium 400 μg kg\(^{-1}\) or gallamine 1000 μg kg\(^{-1}\) were administered by bolus injections at time intervals of respectively 45, 120, 60, 60 and 180 min to avoid accumulation. After the administration of the neuromuscular blocking agents (within 5 s), arterial blood samples were taken at the time when twitch tension approached 50% of control. The bile salts taurocholate (Fluka A. G.) and chenodeoxycholate (Falk GmbH & Co.), were administered by continuous infusion during the 8 min preceding the bolus injection of the neuromuscular blockers. The bile salts were infused at a rate of 40 μmol min\(^{-1}\) and 20 μmol min\(^{-1}\) respectively through the catheter placed in the portal vein. Arterial blood samples were taken for measurement of the plasma concentrations of total bile salt, just before the administration of the neuromuscular blocking agents.

**Analysis of the quaternary ammonium compounds and of the plasma bile salts**

Total bile salt concentrations in the plasma were measured with an enzymatic kit for spectrofluorimetric end-point determinations (Sterognost-3α Automated, Nyegaard & Co. AS, Oslo, Norway). 3α-Hydroxysteroid dehydrogenase transforms the 3α-hydroxyl group on steroids of the C19, C21 and C24 series into their corresponding keto forms, with subsequent generation of NADH from NAD (Mashige, Imai and Osuga, 1976; Osuga et al., 1977). The reduction equivalents of NADH are transferred by the enzyme diaphorase to the fluorogen resazurin, whereby the fluorophore resorufin is generated and measured with an Aminco-Bowman Spectrofluorimeter (Am. Instr. Comp.): excitation 565 nm and emission 580 nm. Spectrofluorimetric determinations of pancuronium, Org 6368, hexafluorenium, and gallamine have been described in detail elsewhere (Meijer, Vermeer and Kwant, 1971; Kersten, Meijer and Agoston, 1973; Agoston et al., 1977; Agoston et al., 1978).

The fluorimetric method to measure steroidal bis-quaternary ammonium compounds in plasma does not discriminate between pancuronium, Org 6368 and their deacetylated metabolite(s). However, the duration of action of the major metabolite of pancuronium bromide (3-OH derivative) does not differ significantly from that of pancuronium (Miller et al., 1978).

**Statistics**

All values are given as mean values ± SEM. Statistical significance was tested using either the paired or the unpaired Student’s \( t \) test with a 95% significance level.

**RESULTS**

**Org 6368**

There was a significant hepatic first-pass clearance of Org 6368, as shown by the differences in intensity and of duration of action of this drug on
the tibialis anterior muscle after its intraportal injections compared with i.v. injections (fig. 1, tables I and II).

The primary bile salts taurocholate and chenodeoxycholate, infused at a rate of respectively 40 and 20 μmol min⁻¹ over 8 min before the administration of the neuromuscular blocking drugs, inhibited the hepatic first-pass clearance of Org 6368 (fig. 1; tables I and II). This can be inferred from the prolongation of and increase in the intensity of the neuromuscular blockade of Org 6368 after the infusion of bile salt compared with control values after both intraportal and i.v. injections of Org 6368. This effect of the two primary bile salts was reversible. Plasma concentrations of taurocholate and chenodeoxycholate at the moment of injection of Org 6368 showed 50–100-fold increases compared with the normal bile salt concentrations in plasma (tables I and II). The concentrations of Org 6368 at 50% recovery of twitch tension, during the increase in plasma bile salt concentrations, did not reveal significant dif-

![Fig. 1. Influence of taurocholate on the pattern of action of Org 6368 in the cat. A = i.v. injection of Org 6368; B = intraportal injection of Org 6368; C = intraportal injection of Org 6368 immediately after intraportal infusion of TC* 320 μmol in 8 min; D = intraportal injection of Org 6368; E = i.v. injection of Org 6368; F = i.v. injection of Org 6368 immediately after intraportal infusion of TC* 320 μmol in 8 min; G = i.v. injection of Org 6368.](image)

**Table I. Neuromuscular blockade, duration of action to 90% recovery of control twitch tension, plasma concentration of the neuromuscular blocker at 50% recovery and plasma concentration of taurocholate just before administration of Org 6368. —=Not measured; 0=not measurable. *Significant difference from i.v. controls; **Significant difference from intraportal controls; ***Significant difference from i.v. controls**

<table>
<thead>
<tr>
<th>Administration</th>
<th>Org 6368 100 μg/kg body wt</th>
<th>Maximal neuromuscular blockade (%)</th>
<th>Duration of action (min)</th>
<th>Org 6368 concentration at 50% recovery (μmol litre⁻¹)</th>
<th>Taurocholate concentration (μmol litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.v.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraportal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+ taurocholate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraportal</td>
<td></td>
<td>53 ±17**</td>
<td>5.5 ±1.6**</td>
<td>0.35</td>
<td>363.3 ±78.2</td>
</tr>
<tr>
<td>Intraportal</td>
<td></td>
<td>5 ±3*</td>
<td>0.1 ±0.1*</td>
<td>0</td>
<td>6.6 ±3.8</td>
</tr>
<tr>
<td>I.v.</td>
<td></td>
<td>52 ±12</td>
<td>4.3 ±0.9</td>
<td>0.30</td>
<td>1.5 ±0.9</td>
</tr>
<tr>
<td>I.v.</td>
<td></td>
<td>83 ±6***</td>
<td>8.9 ±1.1***</td>
<td>0.36 ±0.06</td>
<td>—</td>
</tr>
<tr>
<td>(± taurocholate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I.v.</td>
<td></td>
<td>61 ±9</td>
<td>4.2 ±0.4</td>
<td>0.47 ±0.07</td>
<td>—</td>
</tr>
</tbody>
</table>
Table II. Neuromuscular blockade, duration of action to 90% recovery of control twitch tension, plasma concentration of the neuromuscular blocker at 50% recovery and plasma concentration after chenodeoxycholate just before administration of Org 6368. — = Not measured. *Significant difference from i.v. controls; ** significant difference from intraportal controls; *** significant difference from i.v. controls.

<table>
<thead>
<tr>
<th>Administration Org 6368 100 μg kg⁻¹ body wt</th>
<th>Maximal neuromuscular blockade (%)</th>
<th>Duration of action (min)</th>
<th>Org 6368 concentration at 50% recovery (μmol litre⁻¹)</th>
<th>Chenodeoxycholate concentration (μmol litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.v.</td>
<td>79 ± 14</td>
<td>4.5 ± 0.8</td>
<td>0.19 ± 0.01 (n = 3)</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>Intraportal</td>
<td>33 ± 15*</td>
<td>2.7 ± 0.7*</td>
<td>0.24</td>
<td>—</td>
</tr>
<tr>
<td>Intraportal (+ chenodeoxycholate)</td>
<td>68 ± 11**</td>
<td>5.5 ± 0.7**</td>
<td>0.30 (n = 2)</td>
<td>174.5 ± 63.0</td>
</tr>
<tr>
<td>Intraportal</td>
<td>14 ± 11*</td>
<td>0.9 ± 0.9*</td>
<td>0.33 (n = 1)</td>
<td>9.2 ± 5.2</td>
</tr>
<tr>
<td>i.v.</td>
<td>85 ± 9</td>
<td>6.1 ± 1.1</td>
<td>0.25 ± 0.03 (n = 4)</td>
<td>8.2 ± 5.0</td>
</tr>
<tr>
<td>i.v. (+ chenodeoxycholate)</td>
<td>92 ± 5</td>
<td>8.2 ± 0.7***</td>
<td>0.24 ± 0.03 (n = 4)</td>
<td>—</td>
</tr>
<tr>
<td>i.v.</td>
<td>87 ± 6</td>
<td>6.2 ± 0.6</td>
<td>0.25 ± 0.01 (n = 4)</td>
<td>—</td>
</tr>
</tbody>
</table>

ferences compared with the control situations (tables I and II).

Pancuronium

Intraportal injections of pancuronium gave neuromuscular blockades that were not significantly less than those obtained after i.v. injections (fig. 2, table III).

After the infusion of taurocholate 40 μmol min⁻¹ for 8 min there was a significant increase in the duration of action of pancuronium compared with the neuromuscular blockades after the intraportal control injections (fig. 2, table III).

Org NC 45 and hexafluorenium

In contrast to pancuronium, Org NC 45 and hexafluorenium showed a significant hepatic first-pass clearance when injected intraportally (figs 3 and 4, tables III and IV).

The infusion of taurocholate caused significant increases of neuromuscular blockade and duration of action of Org NC 45 and a significant increase of neuromuscular blockade of hexafluorenium. There was also slight prolongation of the duration of action of hexafluorenium compared with the intraportal control injections (fig. 4, table IV).

Fig. 2. Influence of taurocholate on the pattern of action of pancuronium bromide in the cat. A = i.v. injection of pancuronium; B = intraportal injection of pancuronium; C = intraportal injection of pancuronium immediately after intraportal infusion of TC* 320 μmol in 8 min; D = intraportal injection of pancuronium; E = i.v. injection of pancuronium.
Table III. Neuromuscular blockade, duration of action to 90% recovery of control twitch tension and plasma concentration at 50% recovery. * Significant difference from i.v. controls; ** significant difference from intraportal controls

<table>
<thead>
<tr>
<th></th>
<th>Maximal neuromuscular blockade (%)</th>
<th>Duration of action (min)</th>
<th>Concentration at 50% recovery (μmol litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–25 μg/kg body wt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I.v.</td>
<td>94 ± 4</td>
<td>16.5 ± 0.6</td>
<td>0.027 ± 0.007</td>
</tr>
<tr>
<td>Intraportal</td>
<td>85 ± 12</td>
<td>15.0 ± 1.5</td>
<td>0.041 ± 0.011</td>
</tr>
<tr>
<td>Intraportal (+ taurocholate)</td>
<td>98 ± 2</td>
<td>20.5 ± 1.6**</td>
<td>0.027 ± 0.004</td>
</tr>
<tr>
<td>Intraportal</td>
<td>85 ± 13</td>
<td>17.0 ± 2.2</td>
<td>0.027 ± 0.008</td>
</tr>
<tr>
<td>I.v.</td>
<td>95 ± 4</td>
<td>17.2 ± 1.3</td>
<td>0.041 ± 0.016</td>
</tr>
<tr>
<td>Org NC45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–45 μg/kg body wt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I.v.</td>
<td>93 ± 5</td>
<td>13.6 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Intraportal</td>
<td>57 ± 25</td>
<td>9.5 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Intraportal (+ taurocholate)</td>
<td>82 ± 20**</td>
<td>16.8 ± 4.4**</td>
<td></td>
</tr>
<tr>
<td>Intraporal</td>
<td>48 ± 24*</td>
<td>9.5 ± 3.9</td>
<td></td>
</tr>
<tr>
<td>I.v.</td>
<td>86 ± 14</td>
<td>14.2 ± 3.3</td>
<td></td>
</tr>
</tbody>
</table>

Gallamine

The neuromuscular blocking effect of intraportally administered gallamine was not influenced significantly by the infusion of taurocholate, neither in depth nor in duration (table IV).

The concentrations of pancuronium, hexafluorenium and gallamine after the infusion of bile salt at 50% recovery of twitch tension showed no significant changes compared with the control injections (tables III, IV).

DISCUSSION

The neuromuscular blockade after the second intraportal control injections of Org 6368, Org NC 45 and hexafluorenium tended to be smaller than the blockade following the first intraportal control injections. However, these decreases were of minor importance (tables I–IV).
caused by the increased concentrations of bile salt, can be explained by various mechanisms.

(a) A possible peripheral effect of bile salts on neuromuscular transmission or muscle contraction leading to a potentiation of the action of the neuromuscular blockers under study. This seems to be an unlikely explanation, since the plasma concentrations of the neuromuscular blockers at 50% block during the recovery phase with high concentrations of plasma bile salts were similar to the control values.

(b) Decreased renal clearance. Renal failure as the cause of the prolonged action because of the infusion of bile salt is not very likely, because...
urinary excretion of Org 6368 in the cat is a relatively unimportant route of elimination (10% of the dose in 8 h (Agoston et al., 1977; Westra et al., 1980)). This conclusion is supported by the finding that the neuromuscular blocking effect of gallamine, which is eliminated mainly by the renal route in the cat (67% of the dose in 8 h (Westra et al., 1980)), was not influenced by taurocholate infusion.

(c) Decreased metabolism. Biotransformation patterns of Org 6368 and pancuronium in cats during extrahepatic cholestasis with pathologically increased plasma concentrations of bile salt did not show any difference from the control cats (Westra et al., 1980). Meijer, Vermeer and Kwant (1971) found that hexafluorenium is excreted unchanged in man and rat. These observations make decreased metabolism as a possible mechanism for the observed effects very unlikely.

(d) Decreased biliary excretion. Inhibition of biliary excretion of the neuromuscular blockers by bile salts would hardly contribute to a prolonged duration of action since biliary excretion of Org 6368 and pancuronium was only modest for both compounds in cats in spite of the rapid hepatic uptake (Agoston et al., 1977; Westra et al., 1980).

(e) Decreased hepatic uptake. Distribution into the liver is the only remaining step in the overall hepatic elimination process which could be impaired by bile salts. This conclusion is supported by the finding of a clearly decreased liver to plasma partition ratio for Org 6368 and pancuronium in cats during extrahepatic cholestasis (Westra et al., 1980). The plasma concentrations of bile salt observed following extrahepatic cholestasis (mean 521 µmol litre⁻¹; range 81–794 µmol litre⁻¹) are in the same range as found after the infusion of bile salt in the present study (Westra et al., 1980). The bile salts do not appear to displace the neuromuscular blockers from binding sites in the liver since infusion of bile salts does not lead to blockade of the neuromuscular blockers after preloading the liver (unpublished observations).

These observations support the concept that the site of interaction between bile salts and the neuromuscular blocking drugs Org 6368, pancuronium, Org NC45 and hexafluorenium is probably located at the plasma membrane of the liver cells as was concluded previously for tubocurarine and acetylprocaainamide by Vonk, Scholtens and colleagues (1978) and Vonk, Jekel and colleagues (1978). Inhibition of hepatic uptake by bile salts was observed with agents possessing widely varying molecular structures, such as Org6368, pancuronium, Org NC45, hexafluorenium, tubocurarine and acetylprocaainamide. Although all these agents are organic cations, Org 6368, pancuronium and Org NC45 have a steroidal structure like the bile salts (fig. 5), whereas hexafluorenium, tubocurarine and acetylprocaainamide lack a steroidal configuration.

Also, the hepatic uptake of the organic anion dibromosulphthalein is inhibited by bile salts (Vonk, 1979). This makes it clear that the interaction between bile salts and such compounds is not directly related to a common molecular structure, but is a non-specific yet completely reversible effect of the bile salt. The inhibition of the hepatic uptake of the neuromuscular blockers studied was not associated with significant increases in their plasma concentrations at 50% recovery of twitch tension and is similar to the results reported for dehydrocholate (Vonk et al., 1979).

The lack of influence of bile salts on the action of gallamine is probably a result of its slow hepatic uptake. In cholestatic cats we did not find a significant difference in the liver/plasma concentration ratio whereas 8 h after administration the cumulative biliary excretion of gallamine compared with the control cats (Westra et al., 1980) was also normal.

A possible explanation for the decrease in neuromuscular blockade after the second intra-portal control injections of Org 6368, Org NC45 and hexafluorenium could be an increase in hepatic blood flow following infusion of the bile salt infusion.
The results of the present study demonstrate that infusions of bile salt produce an increase in the duration of action of the recently introduced steroidal neuromuscular blocking drug Org NC45. This effect is between that observed for Org 6368 and pancuronium, indicating that in the cat the liver is probably more important for the removal of Org NC45 from the blood than it is for pancuronium.

ACKNOWLEDGEMENTS

We wish to thank Dr D. S. Savage (Organon Laboratories Ltd, Newhouse) for the supply of Org 6368, Dr H. Falk (Falk GmbH & Co., Freiburg) for the gift of chenodeoxycholate, Mr A. R. de Lange for his technical assistance and Mrs R. van Tilburg for preparing the manuscript.

REFERENCES


SELS BILIAIRES ET AGENTS DE BLOCAGE NEUROMUSCULAIRE

RESUME

On a etudié sur des chats l'influence qu'ont les sels primaires de la bile, le taurocholate et le chénoxycholate, sur le blocage neuromusculaire des médicaments non dépolarisants: Org 6368, pancuronium, Org NC45 et hexafluorenium. On a trouvé qu'ils provoquent après administration des sels biliaires un accroissement des effets de ces agents, lesquels possèdent tous des structures moléculaires très différentes. Les concentrations de sels biliaires dans le plasma ont été similaires à celles obtenues sur les chats après 9 à 10 jours de cholestase extrabéhépatique. L'effet de l'Org NC45, qui est un nouveau analogue monoquaternaire du pancuronium, a été davantage accru que celui du pancuronium. Cet accroissement de l'effet est probablement dû à l'inhibition de la fixation hépatique des agents de blocage neuromusculaire. L'effet de blocage neuromusculaire de la gallamine n'a pas été influencé d'une manière significative par l'administration de sels biliaires.

GALLENSALZE UND NEUROMUSKULÄRE BLOCKIERUNGSMITTEL

ZUSAMMENFASSUNG

Der Einfluss der primären Gallensalze Taurocholat und Chenodeoxycholat auf die neuromuskuläre Blockierung der nichtpolarisierenden Drogen Org 6368, Pancuronium, Org NC45 und Hexafluorenium wurde bei Katzen studiert. Nach Verabreichung der Gallensalze wurde eine Wirkungssteigerung all dieser Drogen beobachtet, die sehr verschiedenartige Molekularstrukturen haben. Die Gallensalz-Plasmakonzentrationen waren ähnlich denen, die sich nach
DRUG INTERACTION WITH BILE SALTS


AGENTES DE BLOQUEO NEUROMUSCULAR Y SALES BILIARES

SUMARIO

Se estudió en gatos la influencia de las sales biliares primarias, taurocolato y queodeoxicolato, en el bloqueo neuromuscular ocasionado por las drogas no despolarizantes, Org 6368, pancuronium, Org NC45 y hexafluoren. Se encontró un incremento de los efectos de estos agentes, todos ellos con estructuras moleculares de gran variación, después de la administración de las sales biliares. Las concentraciones de estas sales en el plasma fueron similares a las obtenidas después de 9 a 10 días de colestasis extrahepática en gatos. El efecto del Org NC45, un nuevo monocuaternario similar al pancuronium, aumentó más que el del pancuronium. Este incremento del efecto es, seguramente, un resultado de la inhibición de la admisión hepática de las drogas de bloqueo neuromuscular. El efecto de bloqueo neuromuscular de la gallamina no quedó significativamente influenciado por la administración de las sales biliares.