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A Model for Determining the Influence of Hepatic Uptake of Nondepolarizing Muscle Relaxants in the Pig

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Hepatic uptake and distribution of nondepolarizing muscle relaxants in pigs was investigated. A portocaval shunt preparation enabled the determination of the pharmacodynamics of nondepolarizing muscle relaxants both during temporary liver exclusion and intraportal injection in the same animal. To demonstrate the validity of the model in pigs, in a pilot study the influence of hepatic uptake on neuromuscular blockade by pancuronium (n = 3) and its congener Org 6368 (n = 3) was determined. Thereafter, the influence of hepatic uptake on neuromuscular blockade by gallamine (3.4 mg/kg, n = 5), Org 6368 (0.3 mg/kg, n = 5), and vecuronium (0.1 mg/kg, n = 4 and 0.15 mg/kg, n = 5) was studied in pigs anesthetized with pentobarbital. Each pig received one relaxant, which was injected four consecutive times under different conditions. The first injection was into the jugular vein (iv) the second into the portal vein, the third was iv while the liver was excluded for 10 min and the fourth was iv (control). After each injection the onset time, intensity, recovery rate, and total duration of neuromuscular blockade were measured. These variables were compared between the four injections for each relaxant. In the pilot study the influence of hepatic uptake on neuromuscular blockade was similar for pancuronium and Org 6368. For gallamine the onset time, intensity, recovery rate, and duration of action were similar after all four injections. For Org 6368 the variables of neuromuscular blockade were similar after iv and intraportal injection, but exclusion of the liver prolonged the neuromuscular block. For both doses of vecuronium intraportal injection resulted in a significant decrease of the intensity of neuromuscular blockade and a shorter duration of action. In contrast, hepatic exclusion enhanced the intensity of neuromuscular blockade and resulted in a prolongation of the duration of action. These results are comparable to data in humans for gallamine the neuromuscular effects of which are not dependent on liver uptake and metabolism, whereas the neuromuscular effects of vecuronium are influenced by liver uptake. These results suggest that the anesthetized pig is suitable for studying the influence of liver uptake and distribution on neuromuscular effects of muscle relaxants. (Key words: Pharmacology: pharmacokinetics. Liver: pharmacokinetics. Neuromuscular relaxants: gallamine; Org 6368; pancuronium; vecuronium.)

HEPATIC UPTAKE, metabolism, and biliary excretion determines the disposition and neuromuscular effects of *d*-tubocurarine,[1,2] pancuronium,[3] and vecuronium.[4,5] In contrast, these processes do not influence the neuromuscular effects of gallamine as was demonstrated in patients with total biliary obstruction.[6] Apart from *in vitro* studies of the isolated perfused liver[7,8] and hepatocytes,[9] few techniques are available for examining the role of the liver in the intact animal, which may predict results in humans. Recently, however, an *in vivo* technique was described for studying the relation between liver uptake and metabolism of pancuronium and its congener Org 6368 and their neuromuscular effects in anesthetized cats.[10] Using a portocaval shunt, the effects of iv injections of nondepolarizing muscle relaxants with and without hepatic exclusion, as well as the effects of intraportal injection, can be compared in the same animal. Org 6368 is structurally similar to pancuronium, the only difference being the replacement of the C-17 acetoxy substituent in pancuronium by hydrogen. In the rat and the cat the onset of action was more rapid and the duration of action was shorter after iv injections of Org 6368 than after pancuronium.[11] This is largely due to the extensive initial uptake (similar to a first pass effect) and metabolism by the cat liver,[12] as was also demonstrated after intraportal injection.[10] Although in humans the onset of action of Org 6368 was more rapid than that of pancuronium, the durations of action were similar.[13] This suggests that there are differences in hepatic uptake and metabolism between the cat and humans.

The pig and human liver are similar because of similarities in the cardiovascular[14,15] and liver enzyme systems[16] of the two species. In addition, as in humans outflow obstruction to hepatic blood flow does not occur in the pig and the pig liver tolerates short periods of ischemia.[17] Perhaps the pig may provide more reliable neuromuscular blocking time course data than that derived from cats. Therefore, we sought to compare in pigs the influence of hepatic uptake and distribution on the neuromuscular effects of pancuronium and Org 6368 (pilot study). Using a similar preparation, the study was extended to gallamine and vecuronium, muscle relaxants

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with large differences in hepatic uptake and metabolism in humans.[5,6]

Methods

Pilot Study (Pancuronium and Org 6368)

After approval by the local animal care committee six Yorkshire pigs, 2–4 months old, weighing 20–30 kg were studied. Anesthesia was induced with azaperone (1 mg/kg im), (Stressnil® Janssen; a butyrophenone used to induce anesthesia in pigs), etomidate (20 mg/kg intraperitoneally), and atropine (0.05 mg/kg im). The tracheae were intubated and the lungs were ventilated with nitrous oxide 66% in oxygen by a Pulmomat respirator adjusted to maintain normocarbia. Anesthesia was maintained with iv pentobarbital (4–8 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}). Rectal temperature was maintained between 36°–37° C with a heating mattress. A carotid artery and two internal jugular veins were cannulated for measurement of arterial blood pressure, injection of drugs, and sampling of blood, respectively.

After laparatomy a side-to-side portocaval shunt was made; the shunt was occluded with a bulldog clamp. Tourniquets were placed around the portal vein between the shunt and the liver and around the common hepatic artery before it branches in arteries such as the gastroduodenal artery. Thus, collateral flow through the latter and other branches was prevented. Because further collateral flow may still be possible through anastomoses between small branches of the left gastric artery and the common hepatic artery between the liver and the diaphragm, these anastomoses were disrupted. The liver could be excluded if the touniquets were tightened and the shunt was opened by removing the clamp.

The force of contraction of the flexor digitorum muscle in a forelimb in response to supramaximal stimulation of the median nerve (frequency 0.1 Hz, duration 0.15 ms) was quantified by means of a Statham UC3 force displacement transducer and recorded. To study the relationship between liver uptake and distribution and the neuromuscular effects of pancuronium (0.045 mg/kg, n = 3) and Org 6368 (0.3 mg/kg, n = 3), these drugs were injected four times with at least 1 h intervals between injection. Each pig received only one muscle relaxant. The first injection was into the jugular vein (iv) with normal liver blood flow. The second injection was into the portal vein with normal liver blood flow. Immediately before the third iv injection the bulldog clamp was removed from the shunt and the hepatic artery and portal vein were occluded. This period of hepatic exclusion was maintained for 10 min, after which the tourniquets were removed and the clamp was placed on the shunt again. The fourth injection was again iv and served as a control. After each injection the onset time of action (time from the end of the injection until maximal depression of twitch height), intensity of neuromuscular block (the percentage depression of the twitch height compared to control), total duration of action (time from the end of the injection to 90% recovery of the twitch height), and the recovery index (time between 25% and 75% recovery of the twitch height) were measured. To assess the effects of the preparation of the portocaval shunt itself, liver biopsies were taken up to 48 h after hepatic exclusion and kept in isotonic saline awaiting microscopic examination later. Thereafter the pigs were killed by injecting an overdose of thiopental.

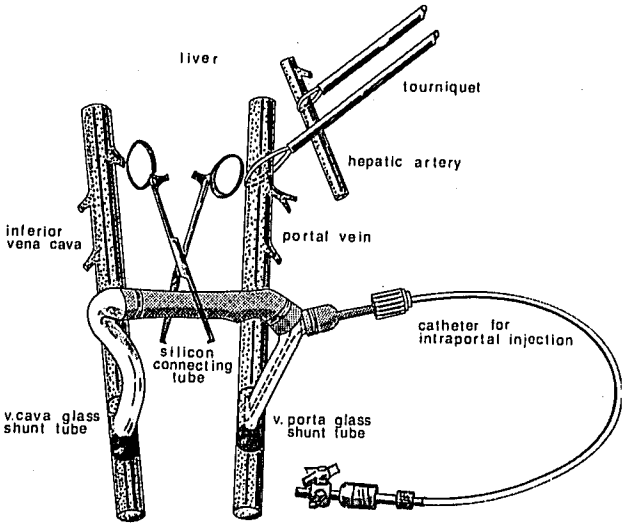

FIG. 1. Schematic presentation of the portocaval shunt.

Org 6368, Gallamine, and Vecuronium

After approval by the local animal care committee 19 German landrace pigs, 2–4 months old and weighing 22–30 kg, were studied. After premedication with atropine (0.02 mg/kg im), azaperone (1 mg/kg im), and etomidate (3–4 mg/kg im) anesthesia was induced in each pig with pentobarbital 10 mg/kg iv and the trachea was intubated. The subsequent conditions of the experiments were similar to those described above.

After a median laparatomy the inferior caval and portal veins and the common hepatic artery were isolated. Glass tubes were inserted into the portal and the inferior caval veins. These tubes were interconnected with a silicone, heparin-coated tube with a diameter equal to that of the glass tubes (fig. 1). Tourniquets were placed around the portal vein between the glass tube and the liver and around the common hepatic artery. This portocaval shunt was closed if the silicone tube was clamped. By removing

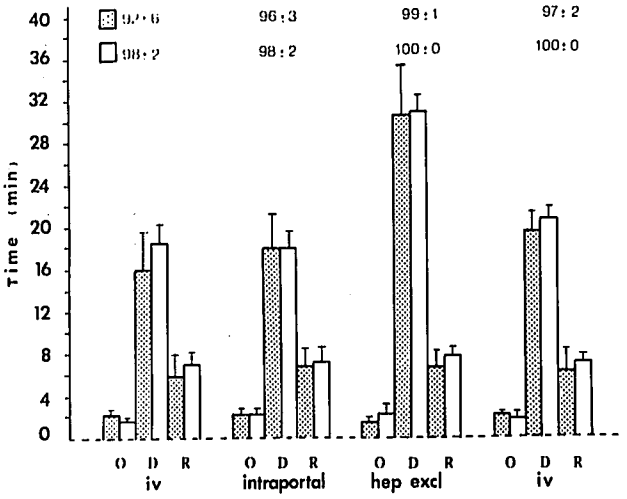

FIG. 2. Neuromuscular effects after pancuronium 0.045 mg/kg (□, open squares) and Org 6368 0.3 mg/kg (□, dotted squares). O = onset time of action; D = duration of action; R = recovery index. Values in the upper half of the figure represent maximum degree of neuromuscular block. Data represent mean ± SD.

the clamp and tightening the tourniquets, the shunt was opened and the liver was excluded. Additional blood supply to the liver was prevented as described above. This preparation allowed the portal blood to drain into the inferior caval vein during the time of total hepatic exclusion. To prevent formation of clots in the shunt heparin (0.3 mg/kg) was administered. A period of 30–45 min was allowed to obtain baseline recordings.

The neuromuscular effects of approximate ED_{95} doses of Org 6368 (0.3 mg/kg, n = 5), gallamine (3.4 mg/kg, n = 5), vecuronium (0.15 mg/kg, n = 5), and of the ED_{40} dose of vecuronium (0.1 mg/kg, n = 4) were studied under the conditions as described above. These doses have been determined to be ED_{95} and ED_{40}, respectively, in preliminary dose–response experiments (unpublished data). The pigs were killed at the end of the experiment by an overdose of thiopental.

For both parts of the study the neuromuscular effects under the various conditions were compared for each drug by Wilcoxon rank-sum test and between the drugs by Kruskal-Wallis ANOVA. Differences were considered significant at a $P < 0.05$.

TABLE 1. Intensity of Neuromuscular Blockade (%) for Org 6368, Gallamine, and Vecuronium after Four Different Injections in the Pig

Drug	N	I	II	III	IV
Org 6368 (0.3 mg/kg)	5	94 (3.6)	90 (4.7)	98 (1.9)	90 (5.7)
Gallamine (3.4 mg/kg)	5	97 (1.9)	97 (1.9)	99 (0.6)	97 (1.9)
Vecuronium (0.1 mg/kg)	4	41 (4.3)	17* (4.2)	66† (4.5)	41 (7.8)
Vecuronium (0.15 mg/kg)	5	95 (2.2)	57* (4.7)	100‡ (0.2)	94 (3.6)

Data represent mean (±SEM). I = iv injection; II = intraportal injection; III = iv injection and liver excluded; IV = control iv injection.
* Different from I, III, and IV ($P < 0.05$).
† Different from I, II, and IV ($P < 0.05$).
‡ Different from II ($P < 0.05$).

Results

PILOT STUDY

The neuromuscular effects of pancuronium and Org 6368 are summarized in figure 2. Hepatic exclusion for 10 min prolonged the duration of action of both drugs ($P < 0.01$). The onset time, intensity, recovery rate, and duration of action were similar for both drugs after iv and intraportal injection. Histologic examinations of liver specimens revealed no damage of liver tissue.

GALLAMINE, ORG 6368, AND VECURONIUM

For gallamine the onset, intensity, recovery rate, and duration of action were similar after all four injections (tables 1 and 2). For Org 6368 these variables were similar after iv and intraportal injection, but exclusion of the liver prolonged the neuromuscular blockade. For both doses of vecuronium intraportal injection resulted in a decrease of the intensity of neuromuscular blockade and a shorter duration of action. In contrast, hepatic exclusion enhanced the intensity of block and prolonged the duration of action. Both the enhancement and the prolongation of the neuromuscular blockade were significantly greater after the smaller (ED_{40} 0.1 mg/kg) than the higher dose (ED_{95} 0.15 mg/kg) of vecuronium. When the ED_{95} doses of Org 6368 and vecuronium were compared, the enhancement of the intensity of block (94–98% and 95–100%, respectively) and the prolongation of the duration of action (11.9–18.9 min and 11.0–19.9 min, respectively) were not significantly different. Figure 3 shows a typical recording of the neuromuscular blockade for vecuronium (0.15 mg/kg) under the four different experimental conditions. The duration and intensity of neuromuscular blockade after the fourth injection were similar to that after the first injection for all drugs.

Discussion

These results suggest that for the study of hepatic uptake and distribution of nondepolarizing muscle relaxants

the pig is better suited than the cat. After equipotent iv doses the duration of action of pancuronium and Org 6368 in the pig was similar to that in humans.[13] Also, in chloralose-anesthetized pigs the relative time course and the magnitude of effect after iv doses of pancuronium, Org 6368, and vecuronium agreed well with our data and data in humans.[18] In contrast, in the cat intensity of neuromuscular blockade was less and the duration of action shorter after Org 6368 than after pancuronium.[10] These species differences are likely to be explained by a more extensive liver uptake of Org 6368 than of pancuronium in the cat[12] *versus* similar uptake of these relaxants by the pig liver as was demonstrated in the pilot study.

The validity of the pig as a model for hepatic uptake of muscle relaxants is supported by our data on the hepatic uptake and distribution of vecuronium and gallamine. Hepatic exclusion prolonged the duration of action of vecuronium. However, intraportal injection decreased both the intensity and the duration of neuromuscular blockade. Apparently, intraportal injection resulted in a considerable first pass hepatic uptake analogous to the first pass effect of drugs given orally. It is possible that due to its monoquarternary structure vecuronium enters the hepatocytes more readily than pancuronium and Org 6368.[19] After vecuronium is taken up by the liver it is possibly metabolized, stored in special organelles,[2] and secondarily released into the bile. In humans as much as 75% of an iv dose of vecuronium may be excreted into the bile.[20] The pharmacokinetics of vecuronium are altered in patients with liver cirrhosis[21] and cholestasis.[22] These results suggest that liver uptake, metabolism, and biliary excretion play an important role in the neuromuscular effects of vecuronium. In contrast to our data in the pig, the intraportal injection of vecuronium in the cat did not influence neuromuscular blockade, whereas hepatic exclusion increased the duration of action.[4] Comparisons between first pass hepatic uptake in the pig and humans *versus* the cat and humans are speculative because the time course of vecuronium-induced neuromuscular blockade after intraportal injection is not known. The lack of influence of hepatic exclusion on the neuromuscular effects of gallamine suggests similarities between pigs and humans. In humans gallamine is excreted 98% unchanged into the urine, and only small amounts are recovered from the bile.[23] Impaired liver function in humans due to total biliary obstruction[6,24] or experimental cholestasis[25,26] does not alter the pharmacokinetics and pharmacodynamics of gallamine.

Because we did not measure concentrations of muscle relaxants in biologic fluids, we cannot describe the influence of hepatic exclusion on processes subsequent to hepatic uptake such as metabolism and biliary excretion. If the liver is excluded, an important organ to which muscle relaxants are distributed is excluded. Thus, the volume of distribution is likely to be decreased. For a given dose the plasma concentration of muscle relaxants would increase. This would result in a more rapid onset of block and an increased intensity and duration of action. We

TABLE 2. Duration of Neuromuscular Blockade (min) for Org 6368, Gallamine, and Vecuronium after Four Different Injections in the Pig

Drug	N	I	II	III	IV
Org 6368 (0.3 mg/kg)	5	11.9 (1.2)	10.8 (1.4)	18.9* (0.9)	11.9 (2.5)
Gallamine (3.4 mg/kg)	5	46.0 (3.8)	49.2 (3.4)	48.0 (2.8)	47.3 (1.8)
Vecuronium (0.1 mg/kg)	4	4.0 (0.3)	2.2† (0.4)	10.3* (0.8)	3.7 (0.2)
Vecuronium (0.15 mg/kg)	5	11.0 (1.1)	6.2† (0.6)	19.9* (2.0)	11.8 (0.8)

Data represent mean (±SEM). I = iv injection; II = intraportal injection; III = iv injection and liver excluded; IV = control iv injection.
* Different from I, II, and IV ($P < 0.05$).
‡ Different from I, III, and IV ($P < 0.05$).

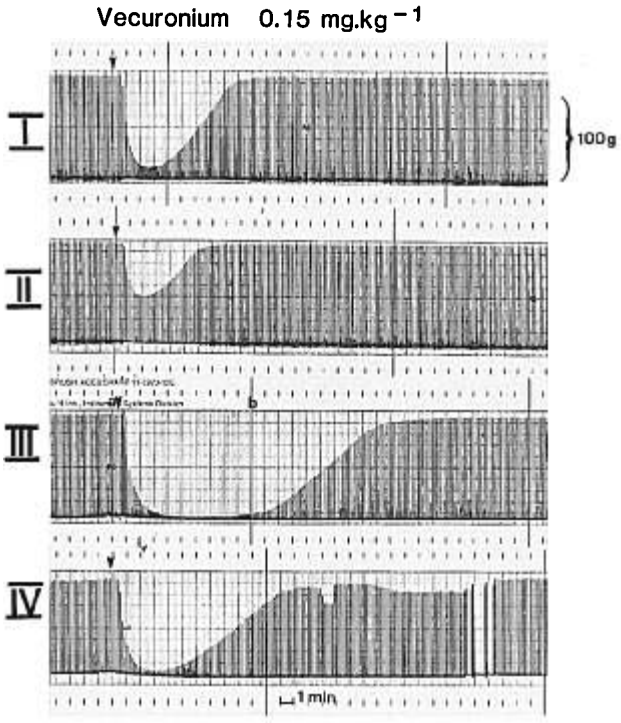

FIG. 3. Recordings of the contraction of pig flexor digitorum muscle in response to supramaximal stimulation of the median nerve and the effects of 0.15 mg/kg vecuronium under various conditions. Trace reads as follows: I = iv injection; II = intraportal injection; III = iv injection during hepatic exclusion; IV = control (iv) injection.

could not demonstrate statistically significant differences in onset of action and intensity of block after equipotent doses of pancuronium, Org 6368, and vecuronium. This may be due to the limited number of pigs studied. However, an increased duration of action was found. Such an increase could not be demonstrated for gallamine. This discrepancy is explained by the relative role of distribution in terminating the effect of these muscle relaxants. For long-acting muscle relaxants, such as gallamine, the duration of action is governed by elimination rather than distribution. Moreover, this contribution of the elimination phase increases with repeated injections.[23] Thus, a decreased distribution due to hepatic exclusion would not be expected to influence the duration of action of gallamine. However, for a short-acting muscle relaxant such as vecuronium, the duration of action is governed by distribution rather than elimination. Thus, hepatic exclusion and decreased distribution would result in a prolonged duration of action. The finding that hepatic exclusion prolonged the duration of action of the ED_{40} (0.1 mg/kg) of vecuronium to a greater extent than that of the ED_{95} (0.15 mg/kg) does not conflict with the above explanation. The lower the dose, the more distribution processes contribute to the termination of action of muscle relaxants.¶ Therefore, a greater influence of hepatic exclusion would be expected.

We further assume that the experimental preparation described in this paper is a useful pharmacologic tool to evaluate the neuromuscular effects of nondepolarizing muscle relaxants during and after hepatic exclusion and after intraportal injection. The viability of the preparation appears to be good: the neuromuscular effects of the muscle relaxants studied after the fourth (control) injection were similar to those after the first injection. In the liver biopsies taken 48 h after each experiment in the pilot study, no histologic evidence of ischemic damage was found. Although only a modest number of animals for each nondepolarizing muscle relaxant have been studied and two different breeds of pig (Yorkshire and German land-race) were used, the value of the data is supported by the fact that the influence of liver uptake and the distribution on the neuromuscular blocking effects of Org 6368 was identical in Yorkshire and German landrace pigs, which could be confirmed in two different labs and the Muir and Marshall's[18] study.

Our data on the influence of hepatic uptake and distribution on the neuromuscular effects of muscle relaxants in the pig do not permit us to predict neuromuscular effects in patients with liver disease such as cirrhosis and cholestasis. At best, our data may predict the time course of neuromuscular blockade during the anhepatic phase of liver transplantation in humans. However, the similarities in hepatic uptake and distribution of nondepolarizing muscle relaxants in humans and pig suggest that the pig could replace the cat for studying the neuromuscular effects of muscle relaxants.

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