The pharmacodynamics and pharmacokinetics of Org 9426, a new non-depolarizing neuromuscular blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl

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The pharmacodynamics and pharmacokinetics of a new non-depolarizing neuromuscular blocking agent, Org 9426, were investigated. Ten patients undergoing elective head and neck surgery and anaesthetized with nitrous oxide, halothane and fentanyl, received a bolus dose of Org 9426 (1 mg · kg^{-1}, 3 × ED_{90}). The isometric contractions of the adductor pollicis muscle following ulnar nerve stimulation (0.1 Hz and intermittent TOF) were measured. Blood and urine were sampled over 8 and 24 hr, respectively. Concentrations of Org 9426 and its possible metabolites in plasma and urine were determined using HPLC. Pharmacokinetic variables were calculated by iterative linear least square regression analysis. Intubation conditions were excellent one minute after administration at a neuromuscular block of 88 (13)% (Mean (CV)). Onset time until maximum block, duration until 25% recovery of twitch height, and recovery from 25 until 75% of twitch height were 1.7 (32), 53 (19) and 20 (37) min, respectively. The TOF reached a ratio of 0.7 after 87 (19) min. Half lives were 1.8 (33), 19 (34), 131 (62) min, respectively, in a three exponential decay; distribution volume at steady-state and plasma clearance were 0.264 (56) L · kg^{-1} and 4.0 (21) ml · kg^{-1} · min^{-1}, respectively. Plasma concentration at 25% recovery of the twitch height was 1.0 mg · L^{-1}. Within 24 h, 33 (37)% of Org 9426 was excreted unchanged in the urine. Metabolites were absent both in plasma and urine. We conclude that the difference in potency between Org 9426 and vecuronium is similar to the difference between their effective concentrations. Org 9426 mimics vecuronium in its time-course of action and pharmacokinetic behaviour and produces excellent intubating conditions one minute following the administration of 1 mg · kg^{-1}.

Nous avons évalué les profils pharmacocinétique et pharmacodynamique d'un nouveau myorelaxant non-dépolarisant, le Org 9426. Lors d'interventions chirurgicales électives sur le cou ou la tête, nous avons injecté 1 mg · kg^{-1} (3 × DE_{90}) d'Org 9426 à dix patients anesthésiés avec du protoxyde d'azote, de l'halothane et du fentanyl. Nous mesurions la réponse isométrique de l'adducteur du pouce à la stimulation du nerf cubital (0,1 Hz et train-de-quatre). Nous mesurions aussi les concentrations d'Org 9426 et de ses métabolites par chromatographie en phase liquide dans des échantillons de sang et d'urine prélevés pendant 8 et 24 h respectivement. Par analyse de régression, nous avons pu tracer le profil pharmacocinétique de l'Org 9426. Une minute après l'injection, les conditions d'intubations étaient excellentes alors que le bloc neuromusculaire était en moyenne de 88%. En moyenne, le temps de latence jusqu'au bloc maximal était de 1,7 min ; sa durée jusqu'à récupération de 25% de la contraction était de 53 min et l'intervalle de récupération 25–75% était de 20 min. Le ratio T_4/T_1 du

Key words

NEUROMUSCULAR RELAXANTS: Org 9426;
PHARMACOKINETICS: distribution, metabolism, urinary excretion;
PHARMACOLOGY: dynamic-kinetic relationship.

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train-de-quatre atteint 0,7 après 87 min en moyenne. Les demi-vies d'élimination d'une courbe tri-exponentielle étaient de 1,8, 19 et 131 min alors que le volume de distribution à l'équilibre était de 0,264 L·kg^{-1} et la clairance plasmatique était de 4,0 ml·kg^{-1} min^{-1}. Au moment où la contraction était revenue à 25% du contrôle, la concentration plasmatique de l'Org 9426 était de 1,0 mg·L^{-1}. En 24 heures, on retrouvait inchangé dans l'urine, 33% de la dose d'Org 9426 mais il n'y avait aucun métabolite dans le sang et dans l'urine. La différence de puissance entre l'Org 9426 et le vécuronium s'explique par le rapport de leurs concentrations efficaces. L'Org 9426 offre un profil pharmacocinétique et d'action temporellement semblable à celui du vécuronium. A raison de 1 mg·kg^{-1}, il offre d'excellentes conditions pour l'intubation de la trachée une minute après l'injection iv.

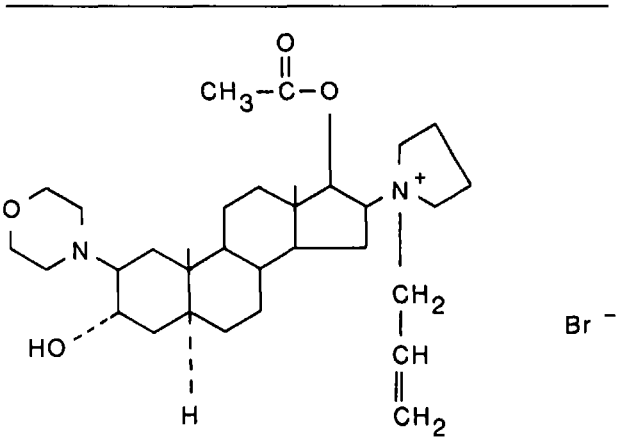

FIGURE 1 Molecular structure of Org 9426.

Org 9426, the 2 morpholino, 16 allyl pyrrolidino, 3 desacetyl derivative of vecuronium, is a new steroidal neuromuscular blocking agent (Figure 1) resembling vecuronium in its time-course of neuromuscular blocking action.[1] In cats and pigs Org 9426 showed 10–20% of the potency of vecuronium.[2] Muscle relaxation developed more quickly and the duration and recovery time were equal or slightly shorter than those of vecuronium. Org 9426 (3 × ED_{90}) in the cat, pig and monkey showed no or only minor changes in heart rate and blood pressure.[3] Cardiovascular studies in dogs revealed no clinically relevant haemodynamic changes.[4] Pharmacokinetic studies in the cat showed that the excretion of Org 9426 was mainly into bile and that renal elimination of this compound was of minor importance.[5] Org 9426, in contrast to vecuronium, is stable in aqueous solution. The most important advantages of this new agent over vecuronium are the more rapid rate of development of block and the good to excellent intubating conditions within one minute after administration of Org 9426, 500 μg·kg^{-1} (± 1.7 × ED_{90}).[1] The aim of this study was to investigate the pharmacodynamic and pharmacokinetic behaviour of Org 9426, 1 mg·kg^{-1}, in healthy patients.

Methods

Patients

The study was approved by the Ethical Committee of the University Hospital of Groningen. Ten patients between 18 and 60 yr old, who were scheduled for head and neck surgery and were ASA physical status I or II, gave written informed consent. No patient received medication known to interact with neuromuscular blocking agents. None suffered from renal disease, neuromus cular disorders or hepatic failure.

Anaesthesia

Patients were given premedication with midazolam 0.1 mg·kg^{-1} orally. After arrival in the operating room an ECG, a blood pressure monitor (Dinamap), and a pulse-oximeter were attached to the patient and two peripheral venous catheters, one in the left and one in the right arm, were introduced for administration of medication and fluids, and for sampling of blood, respectively. Anaesthesia was induced with thiopentone 4–6 mg·kg^{-1} and fentanyl 3–6 μg·kg^{-1} *iv*. The lungs were ventilated with 65% nitrous oxide in oxygen by mask. Org 9426, 1 mg·kg^{-1} *iv*, injected over ten seconds, was administered within three minutes after induction of anaesthesia, followed one minute later by tracheal intubation. After intubation, anaesthesia was maintained with halothane, 0.6% end-tidal concentration, added to 65% nitrous oxide in oxygen, supplemented by small incremental doses of fentanyl. End-tidal gas concentrations were measured by a Capnomac® monitor (DATEX). The $PETCO_2$ was kept between 4 and 4.6 kPa. The body and hand temperatures were measured continuously and kept above 36.5 and 32.5° C, respectively.

Pharmacodynamic measurements

The neuromuscular blocking effects were measured by mechanomyography (Relaxometer, Dept. of Anaesthesiology, University Hospital, Groningen, The Netherlands). The monitor was connected to the awake patient, but the calibration procedure was not performed until after induction of anaesthesia. The ulnar nerve was stimulated at the wrist using supramaximal square wave pulses of 0.2 ms at a rate of 0.1 Hz. The isometric contraction of the adductor pollicis muscle was measured with a force transducer and recorded on line. Onset time (time from the end of Org 9426 injection until disappearance of the twitch response), clinical duration (time from the end of

injection until 25% recovery of the twitch height), recovery index (time between 25 and 75% recovery of the twitch height), and total duration (defined as the time between the end of Org 9426 administration until 90% recovery of the twitch height) were measured. The train-of-four (TOF) ratio (relative magnitude of the fourth to the first twitch height when four consecutive stimuli are given at a frequency of 2 Hz) was used for quantitation of fade during recovery. The TOF ratio was assessed at 25, 75 and 90% recovery of the twitch height and continuously, every 12 sec, as soon as 100% recovery of the twitch height was obtained. The registration was terminated at a TOF ratio of 0.7.

The intubation conditions were scored one minute following administration of Org 9426 according to the scale of Krieg *et al.*[6]

Pharmacokinetic procedures

Blood samples, 4 ml, were collected via a peripheral cannula in the arm opposite to the infusion arm or via a central venous line. Samples were taken prior to and 1, 2, 4, 6, 9, 12, 15, 25, 40, 60, 75, 90, 120, 180, 240, 360 and 480 min after the administration of Org 9426. Additional samples were taken at 25 and 75% recovery of the twitch height. The samples were immediately acidified with 1 ml of NaH_2PO_4 1M to prevent spontaneous deacetylation of Org 9426 and kept at room temperature to prevent haemolysis. The plasma was separated by centrifuge within four hours and kept frozen at −18° C until analysis.

Urine samples were collected from a previously inserted catheter prior to and 2, 4, 6, 9, 12, 18 and 24 hr after the administration of Org 9426. The sampling bag was supplied with 1 ml of NaH_2PO_4 1M at the start of a sampling period to acidify the urine, thereby preventing spontaneous deacetylation of Org 9426 in the bag. After the pH was checked well-mixed aliquots of 10 ml of the collected fractions were frozen until analysis.

The concentrations of Org 9426 and its potential metabolites, 17-desacetyl Org 9426 and des-allyl Org 9426 were analyzed by high performance liquid chromatography (HPLC). With this method the parent compound and the metabolites can be separated. The method has been described for determination of vecuronium[7] and may be applied, after minor modifications, for Org 9426. This modified technique has been validated. After extraction of Org 9426 and its putative metabolites from the biological materials, the compounds were separated by HPLC and determined by fluorimetric measurement following a post-column ion-pair extraction. The HPLC method shows a linear relationship between drug amount and fluorescence in a range of 20–200 ng in the prepared sample. The accuracy and the precision were evaluated by adding known amounts of Org 9426 to blank human plasma of five different patients. The accuracy, given in mean percentages and coefficient of variation between brackets, of 20 and 200 ng Org 9426 were −6 (12)% and −0.1 (5.6)%, respectively. The lowest concentration of Org 9426 or the abovementioned metabolites that can be reliably determined is 5 $ng \cdot ml^{-1}$.

Pharmacokinetic analysis was based on iterative linear least square regression analysis by the computer program RUGFIT.[8] Concentration vs time data were individually fitted to both a two- and a three-compartment model. The appropriate model for each patient was determined by the F test. The volume of the central compartment (V_1), the steady-state distribution volume (V_{ss}), the total plasma clearance (CL), and the area under the curve (AUC) were calculated using standard equations.[8] The microparameters were calculated from a mamillary model. Elimination was assumed to take place from the central compartments.[8] The elimination half-life of Org 9426 was also derived from the fractional amounts of urinary excreted Org 9426 over 24 hr.

Results are presented as mean values and coefficients of variation between brackets, unless otherwise stated.

Results

The group under investigation consisted of seven women and three men with a mean age of 51.4 yr (range 30–60 yr) and a mean weight of 68.8 kg (range 56–75 kg), undergoing various types of surgery in the head and neck region.

Pharmacodynamic effects

The onset and clinical duration of Org 9426, 1 $mg \cdot kg^{-1}$, approximately 3 × ED_{90}, were 1.7 (32) and 53 (19) min, respectively. The recovery index and total duration amounted to 20 (37) and 80 (29) min, respectively. The train-of-four ratio regained the value of 0.7 at 87 (19) min. The neuromuscular block one minute after end of injection of Org 9426 and just before tracheal intubation was 88.3 (13)%. All patients showed excellent intubating conditions.

Pharmacokinetics

The plasma concentration decay of Org 9426 in both groups was best described by a triexponential equation. The variables are presented in Table I as mean values with their coefficients of variation (CV). The microparameters derived from the mean values of the slopes and intercepts are presented in Table II. The plasma concentrations of Org 9426 at 25% and 75% recovery of the twitch height were 1.0 (20) and 0.7 (30) $mg \cdot L^{-1}$, respectively. Metabolites in plasma were absent or at least below the detection limit (5 $ng \cdot ml^{-1}$). The plasma concentration decay curve, based on the mean values of the pharmacoki-

TABLE I Pharmacokinetic variables of Org 9426 following an intravenous bolus dose of Org 9426, 1 mg·kg^{-1} in patients (mean (CV)). The variables from another study* using an equipotent dose of vecuronium, 0.15 mg·kg^{-1}, are included in the table

Variables	*Units*	*Org 9426*		*Vecuronium*	
C_1	mg·L^{-1}	17.540	(45)	1.30	(33)
C_2	mg·L^{-1}	4.7427	(15)	0.77	(90)
C_3	mg·L^{-1}	0.4958	(96)	0.04	(98)
L_1	min^{-1}	0.4382	(43)	0.507	(99)
L_2	min^{-1}	0.0417	(39)	0.052	(45)
L_3	min^{-1}	0.0076	(60)	0.006	(77)
t_{alfa}	min	1.82		1.37	
t_{beta}	min	19.0		13.3	
t_{gamma}	min	131		108	
V_1	L·kg^{-1}	0.045	(29)	0.076	(89)
V_{ss}	L·kg^{-1}	0.267	(56)	0.413	(89)
AUC	mg·min·L^{-1}	264		32.8	
CL	ml·kg^{-1}·min^{-1}	3.97	(24)	4.58	(14)

*Bencini AF *et al.*[11]

The half lives were calculated as $t_{\frac{1}{2}}$ = ln 2/lambda.

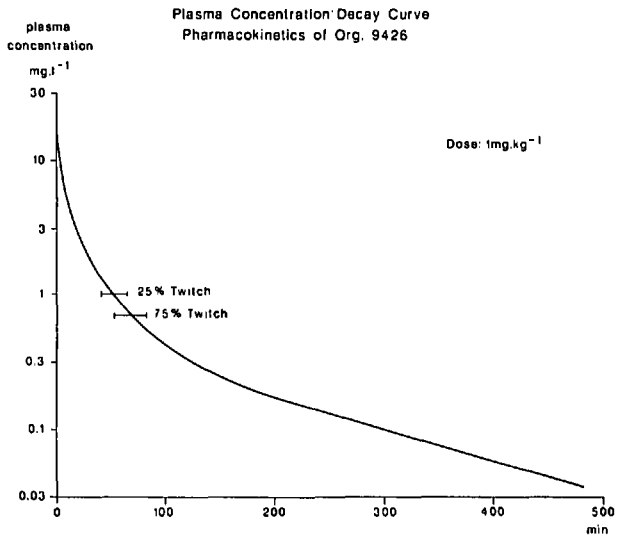

FIGURE 2 Plasma concentration decay curve of Org 9426, based on the calculated mean values of the intercepts and slopes of the group. The mean plasma concentrations at 25 and 75% recovery of the twitch height are given to indicate the concentration–response relationships during recovery of neuromuscular block.

netic variables and the mean concentrations measured at 25 and 75% recovery of the twitch height, were 1.02 (20) and 0.69 (30) mg·L^{-1}, respectively, and are shown in Figure 2.

Urinary excretion of Org 9426 over 24 hr was 33 (37)%. Of the total amount recovered from the urine 65 and 94% were found in the fractions of the first two and over the first six hours, respectively. Metabolites were absent or at least below the detection limit (5 ng·ml^{-1}). A terminal half-life of 162 (32) min could be calculated from the fractional amounts of Org 9426 excreted in time in the urine.

Discussion

Pharmacodynamic effects

After approximately three times the ED_{90} dose of Org 9426, the onset time until 100% block is similar to or slightly shorter than the onset values for almost equipotent doses of vecuronium reported by Krieg[9] (150 μg·kg^{-1}, 1.8 (20) min) or by Agoston[10] (120 μg·kg^{-1}, 2.7 (45) min). The intubation conditions one minute following administration of Org 9426 are identical to the excellent conditions reported two minutes after an equipotent dose of vecuronium, 150 μg·kg^{-1}, in patients under neurolept-anaesthesia.[9] At the time of intubation this dose had produced almost complete disappearance of the twitch height. The recovery indices (15.2 (37)[9] and 15.5 (23)[10] min) and total durations of vecuronium (70 (20)[9] and 60 (16)[10] min) are somewhat shorter than those measured after Org 9426. However, in our study, patients were anaesthetized with a volatile anaesthetic which, to some extent, may have prolonged the recovery index and the duration of action. Taking into account the difference in anaesthetic technique, the time course of action of Org 9426 seems to be similar to that of vecuronium.

TABLE II Microparameters of Org 9426 and vecuronium* calculated using the amount administered (1 mg·kg^{-1}), and the mean values of the intercepts ($C_{1,2,3}$) and the slopes ($L_{1,2,3}$) as presented in Table I

Microparameter	*Units*	*Org 9426*	*Vecuronium*
k_{12}	min^{-1}	0.21	0.22
k_{21}	min^{-1}	0.13	0.23
k_{13}	min^{-1}	0.028	0.023
k_{31}	min^{-1}	0.01	0.008
k_{10}	min^{-1}	0.1	0.09
V_1	L·kg^{-1}	0.044	0.076
V_2	L·kg^{-1}	0.072	0.073
V_3	L·kg^{-1}	0.122	0.208

*Bencini AF *et al.*[11]

Pharmacokinetics

Comparison of the pharmacokinetic variables of Org 9426 and vecuronium indicates similarity between the compounds with the exception of the values for distribution volumes. The smaller distribution volume, V_{ss}, of Org 9426 may be a reflection of the lower lipophilicity of this compound compared with vecuronium (own unpublished data). The Octanol/Krebs partition coefficients for Org 9426 and vecuronium amount to 0.5 and 2.5, respectively.

The difference in the central volume, V_1, may also be related in part to a difference in rate of administration of the neuromuscular blocking drugs in these studies. The bolus of vecuronium was administered over two minutes, whereas the administration of Org 9426 was over ten seconds. The slow bolus may have resulted in a somewhat decreased C_l and increased V_1 value for vecuronium, despite the fact that the fitting procedure does take the rate of administration into account.

The plasma concentrations of vecuronium at 25% and 75% recovery of twitch height following an equipotent dose[12] were 0.13 (15) and 0.08 (25), respectively. The concentrations of Org 9426, as measured at certain twitch heights during recovery of neuromuscular block, are eight times higher than identical concentrations of vecuronium. This difference, approaching the difference in effective concentrations between both compounds (EC_{75} and EC_{25}), indicates that the difference in potency (ED_{90}), i.e., Org 9426 is 6–7 times less potent than vecuronium,[1] is mainly due to a difference in pharmacodynamics such as affinity of the drug for the receptor. A pharmacokinetic factor, for example a difference in initial clearance between both drugs, is unlikely to be responsible for the difference in potency since the sum of the rate constants k_{12}, k_{13}, and k_{10} for Org 9426 and vecuronium reveal identical values, i.e., 0.338 vs 0.333 min^{-1}, respectively (Table II).

Our study also suggests a limited contribution of renal excretion to the elimination of Org 9426, for after six hr only limited amounts are still found in the urine. Besides, the fraction of Org 9426 excreted into the urine in 24 hr is similar to that of vecuronium (±30%), a drug that primarily is eliminated by biliary excretion as was shown by Bencini et al.[13] Results from pharmacokinetic studies of Org 9426 in the cat[5] show that plasma clearance of Org 9426 is also primarily due to liver uptake and biliary excretion. More than 50% of Org 9426 was excreted into the bile within six hours, the majority within one hour following administration of the drug. This amount was the same in cats with and without ligated renal pedicles. Renal elimination in cats accounted only for less than 9% over the same interval of six hours. Liver content after six hours amounted to 36 and 47% in the normal cats and the cats with ligated renal pedicles, respectively. Increase in liver storage appears, therefore, to replace the loss of renal function in these cats. This could imply that renal insufficiency may have little influence on the time course of neuromuscular blocking effects of a bolus dose of Org 9426 if administered within the clinical dose range.

The absence of measurable amounts of metabolites is in accordance to the findings in cats,[5] where metabolites were absent in plasma and urine, as well as in bile.

Conclusions

- Org 9426, 1 $mg \cdot kg^{-1}$, when compared with an equipotent dose of vecuronium, shows a similar time course of neuromuscular blocking action. The intubation conditions one minute following the administration of this dose of Org 9426 are excellent.
- The pharmacokinetic behaviour of Org 9426 is identical to that of vecuronium. However, the volume of distribution of Org 9426 appears to be smaller.
- The difference in potency between vecuronium and Org 9426 seems to be mainly due to a lower affinity of Org 9426 for the nicotinic receptor of the neuromuscular junction. The plasma concentration of Org 9426 at 25% recovery of the twitch height is approximately eight-fold higher than that of vecuronium.

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