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Effect of Thermal Injury on the Pharmacokinetics and Pharmacodynamics of Atracurium in Humans

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Thermal injury causes resistance to many nondepolarizing muscle relaxants including *d*-tubocurarine, metocurine, pancuronium, and atracurium. To evaluate the role of pharmacokinetics and pharmacodynamics in this phenomenon, the disposition and effect of atracurium (0.5 mg/kg iv) were studied in thermally injured patients (5 males, 16–43 yr) in comparison with that in nonburned control patients (3 males, 1 female, 24–53 yr). The decline of plasma atracurium concentration with time was biexponential in both groups of patients. There were no significant differences in the mean value of any pharmacokinetic parameter (clearance, V_1, V_β, α and β half-lives). The time course of effect was also similar, although the maximum twitch depression was significantly smaller (66.1% *vs.* 100% maximal twitch depression) and time to recover to 50% of maximal twitch depression was significantly shorter (14.2 *vs.* 52 min) in thermally injured patients. Patients with thermal injury had an EC_{50} (plasma concentration of atracurium required for 50% of the maximum possible response) 3.4 times that of control patients. Plasma-free fraction of atracurium in the thermally injured patients was 75% that in controls, and free EC_{50} (the product of free fraction and EC_{50}) of the thermally injured group was 2.7 times that of controls. The results of this study confirm a pharmacodynamic mechanism for the majority of resistance to atracurium, with a diminished free fraction in plasma also contributing to this effect. (Key words: Anesthesia, burns: pharmacokinetics; pharmacodynamics. Neuromuscular relaxants: atracurium. Pharmacodynamics: atracurium. Pharmacokinetics: atracurium.)

THERMAL INJURY causes resistance to many non-depolarizing muscle relaxants including *d*-tubocurarine (*d*Tc),[1] metocurine,[2] pancuronium,[3] and atracurium.[4] The degree of resistance varies with time (not present for the first week after injury and peaks about 5–6 weeks after injury) and size of burn (approximately 30% or more of total body surface area must be injured to produce resistance).[3,4] Studies with metocurine and *d*-Tc have implicated the role of a pharmacodynamic mechanism of resistance but have not ruled out a pharmacokinetic contribution in patients shown to be resistant at the time of the study.[1–3,5,6]

We studied the disposition and effect of atracurium in thermally injured patients to evaluate the contribution of pharmacokinetic- and pharmacodynamic-based mechanisms to the resistance to atracurium reported previously.

Methods

This study was approved by the Human Subjects Review Committee of the University of Washington. Five patients who had suffered burns involving 24–95% of total body surface area were studied at surgery for burn wound excision and skin grafting 10–46 days postinjury. All were males, and their ages ranged from 16 to 43 yr. A control group of 3 males and 1 female, ASA physical status 1, 24–52 yr of age undergoing extremity surgery resulting in less than 200 ml blood loss was also studied. Patient characteristics are summarized in table 1.

To measure the degree of neuromuscular blockade, the upper extremity was immobilized and the strength of contraction in the adductor pollicis was measured by linking the thumb to a Grass FT10® force transducer. The ulnar nerve was stimulated *via* 22-g subcutaneous needle electrodes with a 0.2-ms supramaximal square wave at 2 Hz for 2 s (train-of-four). Stimulation was repeated every 12 s. The displacement was converted to an electrical signal and recorded on a strip chart recorder. Anesthesia was induced with fentanyl 15–25 μg/kg iv over 3 min, followed by a bolus of either 2 mg/kg of sodium thiopental or 1 mg/kg of ketamine. Anesthesia was maintained with nitrous oxide in oxygen by positive pressure ventilation and an infusion of fentanyl of 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$. After induction of anesthesia, 0.5 mg/kg atracurium was injected as a bolus. Arterial blood samples from burned patients and venous blood samples from unburned patients (3 ml) were drawn into heparinized syringes at 3, 6, 9, 12, 15, 20, 30, 45, 60, 75, and 90 min. In unburned patients, the ratio of atracurium concentration (arterial/venous) is 1.11 ± 0.188 (mean ± SD, n = 4) at 6 min after the dose and 0.928 ± 0.124 at 20 min. Neither of these values is statistically significantly different from 1.0 (95% confidence limit includes 1.0). The samples were quickly transferred to polypropylene tubes containing 60 μl 3N HCl to prevent degradation of atracurium in plasma. The *p*H of the thawed plasma sample is approximately 4–5. There is less than 5% degradation of atracurium over 30 min at this *p*H. The plasma was immediately separated and stored in plastic tubes at −80° C until analysis. All twitch tension measurements were made and samples collected before blood loss due to surgery was sustained. No volatile anesthetics were used at any time.

The binding of atracurium to plasma proteins was de-

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termined for each patient. In a preliminary study, plasma-free fraction of atracurium was constant over a tenfold concentration range (0.5–5.0 μg/ml). Plasma samples from each patient were respectively combined to yield a total volume of 2.5 ml, and the *p*H of the plasma was adjusted to 6.2–6.3. This *p*H range was chosen to be acidic enough to prevent rapid degradation of atracurium (5.9% decrease in plasma concentration as determined by high performance liquid chromatography over 30 min at room temperature under these conditions) and to minimally affect plasma protein binding (*i.e.*, a *p*H as high as possible that would maintain stability for the period of measurement was used). A 400-μl aliquot of this *p*H-adjusted plasma was used to determine total atracurium concentration. The remaining plasma (2 ml) was transferred to an Amicon Micropartition system with a YMT® membrane (Micropartition Systems, Amicon, Inc., Danvers, MA) that retains 99.9% of serum proteins (30 KD cutoff) and demonstrates negligible nonspecific binding of atracurium (recovery from filtered buffer was 103% ± 4%, n = 4). Plasma was centrifuged for 25 min, 1,200 × *g*, at room temperature. Protein-free filtrate (400 μl) was combined with 25 μl of the internal standard and atracurium concentration was determined as described below.

Atracurium concentration in plasma and plasma ultrafiltrate was determined by procedure of Stiller *et al.*[7] with modifications. Alcuronium (Hoffman-LaRoche) was added to 0.1N HCl to a concentration of 1 mg/ml and allowed to stand at room temperature for 8 h to allow conversion to a product (not identified) stable in HCl. The reaction apparently reaches equilibrium at 8 h because additional net conversion to product is not observed. This solution was stored at 4° C and diluted 1:5 in 1 mM HCl for analysis. The plasma sample was thawed and 0.5 ml was combined with 25 μl of internal standard solution and applied to a C-18 Sep-Pak® column (Waters). The column was preconditioned with methanol and phosphate buffer (*p*H 5.4). After applying the sample, the column was washed with 2 ml of phosphate buffer followed by 1 ml of methanol:water (60:40). The drug and internal standard were eluted with 1 ml acetonitrile:0.1N HCl (75:25).

High performance liquid chromatography was carried out on a 5-μm C-8 column (Alltech) with a mobile phase consisting of 30 mM tetramethyl ammonium hydroxide (20% solution in methanol) in 30 mM KH_2PO_4 (*p*H 3.0) and acetonitrile (70:30). The system was maintained at ambient temperature and peaks were quantified by fluorescence (235 nm excitation, 310 nm emission, Kratos Analytical). Peak areas were obtained using an HP 3990A integrator. Two standard curves were used to cover the entire concentration range: one from 0.1 to 0.7 μg/ml and the other from 0.7 to 6.0 μg/ml. The assay was linear over the individual ranges, and recovery after extraction was approximately 90%.

TABLE 1. Patient Characteristics

Patient	Age (yr)	Sex	Burn Size (% TBSA)	Time after Injury (days)
Control				
1	52	M	—	—
2	34	F	—	—
3	26	M	—	—
4	24	M	—	—
Mean	34	—	—	—
SD	12.8	—	—	—
Burned				
5	43	M	37	10
6	41	M	28	46
7	39	M	95	30
8	16	M	24	22
9	43	M	61	18
Mean	36	—	49	25.2
SD	11.5	—	29.5	13.7

TBSA = total body surface area; M = male; F = female.

The data were fitted to a pharmacokinetic/pharmacodynamic model[8] with the program BMDP85. Concentration data were weighted $1/C^2$ and effect data were not weighted. The strip chart record of adductor pollicis contraction was also analyzed for percent maximal twitch depression and the time from atracurium bolus to recovery to 50% of the preatracurium twitch force. Statistical comparisons were made by *t*-test with a $P < 0.05$ considered statistically significant.

Results

Figure 1 shows the time course of atracurium concentration and effect in plasma for a burned and a control patient. The decline of atracurium concentration with time is biexponential and follows a similar time course in both patients. The time course of effect is similar in both patients in that the maximum twitch depression is observed soon after the injection of atracurium. However, the maximum twitch depression is 65% and the time to recover to 50% of preatracurium twitch force is 15 min in the burned patient; the values for the control patient are 100% and 48 min.

Table 2 summarizes the response to atracurium. The 0.5-mg/kg dose of atracurium abolished twitch response in the control subjects but caused a mean twitch depression of 66.1% in burned patients. The time to 50% recovery of preatracurium twitch force is also significantly different between burned and control patients, with mean values of 14.2 and 52 min, respectively. These results could have been caused by pharmacokinetic or pharmacodynamic mechanisms.

There was no statistically significant difference in the mean value of any pharmacokinetic parameter (table 3). The results of the pharmacodynamic analysis are shown in table 4. The rate constant k_{eo} is a distributional parameter, which in the model defines the equilibrium state

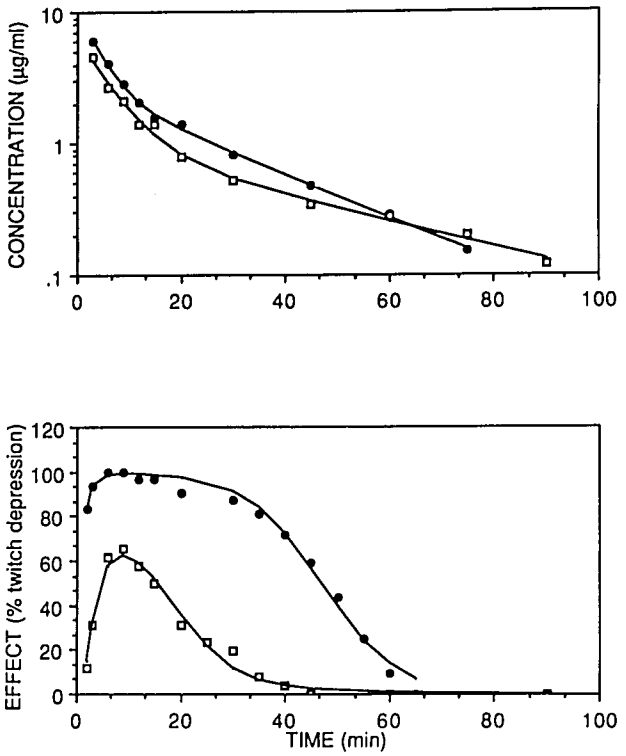

FIG. 1. Time course of atracurium concentration in plasma (upper panel) and effect (lower panel) in patients 6 (burned, □) and 1 (control, ●).

between the central (plasma) and "effect" (biophase) compartments. Burn injury did not alter the value of this parameter. Burn injury also did not alter the value of γ, which is the exponent in the Hill equation and defines the shape (degree of sigmoidicity, γ can be viewed as a slope term) of the relationship between concentration of drug in the effect compartment and response. The thermally injured group had an EC_{50} 3.4 times that of the control group. EC_{50} is the concentration of atracurium in plasma at steady state needed to cause 50% of the maximum possible response (100% twitch depression). Burn injury also caused a 25% decrease in plasma-free fraction of atracurium. Free EC_{50} (*i.e.*, unbound concentration in plasma at steady state required to depress twitch to 50% of maximum possible response, calculated as the product of EC_{50} and free fraction) in the group of burn patients was 2.7 times that of control patients.

TABLE 2. Summary of Response to 0.5 mg/kg Atracurium

Patient	% Maximal Twitch Depression	Time to 50% Recovery of Preatracurium Twitch Force (min)
Control		
1	100	48
2	100	64
3	100	43
4	100	53
Mean	100	52
SD	0	9.0
Burned		
5	87.5	23
6	65.4	15
7	35.7	0
8	87.1	24
9	54.6	9
Mean	66.1*	14.2*
SD	22.1	10.0
P value*	0.027	0.0013

* Compared with control group by *t* test.

TABLE 3. Pharmacokinetics of Atracurium in Patients

Patient	Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	V_1 (ml/kg)	V_β (ml/kg)	α Half-life (min)	β Half-life (min)
Control					
1	4.93	49.1	132	3.05	18.7
2	5.12	87.7	189	6.79	25.6
3	7.44	83.7	180	2.41	16.9
4	5.76	44.8	107	2.26	12.8
Mean	5.81	66.3	152	3.63	18.5
SD	1.13	22.5	39.1	2.14	5.38
Burned					
5	4.47	43.4	136	4.39	21.0
6	6.11	76.0	278	4.15	31.5
7	6.11	48.8	153	2.09	17.3
8	5.59	62.8	140	1.93	17.3
9	4.41	73.4	163	6.93	25.6
Mean	5.34	60.9	174	3.90	22.7
SD	0.84	14.5	59.1	2.04	6.07

V_1 = initial volume of distribution; V_β = volume of distribution at pseudoequilibrium; α and β half-lives = half-lives associated with the initial rapid and later slower decline of atracurium concentration in plasma.

Differences between burn and control groups not significant by *t* test.

Discussion

The clearance, volume of distribution at pseudoequilibrium (V_β) and β half-life of atracurium observed in our

TABLE 4. Pharmacodynamics of Atracurium in Patients

Patient	k_{e0} (min^{-1})	γ	EC_{50} (μg/ml)	Free Fraction	Free EC_{50} (μg/ml)
Control					
1	0.076	3.89	0.814	0.407	0.331
2	0.074	4.20	0.536	0.478	0.256
3	0.100	5.81	0.613	0.587	0.360
4	0.045	4.31	0.714	0.518	0.370
Mean	0.074	4.55	0.669	0.498	0.329
SD	0.022	0.857	0.121	0.075	0.052
Burn					
5	0.082	6.61	2.35	0.364	0.855
6	0.100	3.25	1.76	0.276	0.486
7	0.074	2.71	2.52	0.431	1.09
8	0.107	5.27	1.58	0.363	0.574
9	0.133	2.07	3.12	0.441	1.38
Mean	0.100	3.98	2.27	0.375	0.877
SD	0.023	1.90	0.62	0.066	0.369
P value*	>0.14	>0.14	0.005	0.043	0.030

* Compared with control.

normal subjects are in close agreement with the values reported by other investigators.[8-11] However, the mean value of α half-life observed in the normal subjects (3.63 min) is somewhat greater than that reported by those investigators (approximately 2 min). The difference in α half-life is probably due to more intensive sampling by other investigators soon after atracurium administration. The difference in sampling intensity would also account for the somewhat larger initial volume of distribution found in our control patients (mean, 67 ml/kg) compared with a value of approximately 50 ml/kg usually reported.

The 0.5-mg/kg dose of atracurium completely abolished the twitch response in control patients and a mean of 52 min was required for twitch height to return to 50% of control. These findings are consistent with observations made by others in patients with similar characteristics.[8,9,11] In addition to these gross measures of the effect of a 0.5 mg/kg bolus dose of atracurium, the pharmacokinetic/pharmacodynamic model applied here has been applied previously to atracurium.[8] In that study, patients comparable to those in our control group had an EC_{50} of 652 $\pm$ 23 ng/ml (mean $\pm$ SD), k_{eo} was 0.100 $\pm$ 0.008 min^{-1}, and γ was 4.25 $\pm$ 0.55 determined from single switch stimulation. The respective values in our control group were 670 $\pm$ 120 ng/ml, 0.074 $\pm$ 0.022 min^{-1}, and 4.55 $\pm$ 0.86 (table 4). Thus, the values of both pharmacokinetic and pharmacodynamic parameters determined in our control patients agree well with those previously reported in comparable patients.

The resistance to atracurium previously reported in burned patients was again observed in the burned patients studied here (table 2). There were no differences between groups in pharmacokinetics (table 3). A 3.4-fold increase in the concentration of atracurium required to produce 50% maximal depression of twitch (EC_{50}) accounted for resistance. This difference is substantially greater than the slight difference (perhaps 10% but statistically not significant) that may exist between arterial and venous atracurium concentration. A portion of the degree of resistance reflected in the higher EC_{50} value was accounted for by a decrease in atracurium-free fraction, but the 2.7-fold higher free EC_{50} in the burn group most likely has a pharmacodynamic basis. The increased plasma protein binding of atracurium agrees with the observation made by Leibel *et al.*[6] with regard to *d*-Tc and by Martyn *et al.*[12] with imipramine. The decrease in imipramine free fraction (and by inference, *d*-Tc and atracurium) can be attributed to an increase in plasma α_1-acid glycoprotein (orosomucoid) concentration.[12]

The pharmacodynamic basis for resistance to atracurium following thermal injury agrees with the altered plasma concentration–effect relationship reported by Martyn *et al.* for *d*-Tc[1] and metocurine.[2] Pharmacokinetic changes following burn injury alter the requirements for many drugs eliminated renally; aminoglycoside antibiotics are probably the best example.[13] However, neither pharmacokinetic nor plasma protein binding alterations account for the increased dose requirement following burn injury for *d*-Tc.[1,6]

The mechanism underlying the resistance to nondepolarizing muscle relaxants has been attributed to be an increase in acetylcholine receptors at the neuromuscular junction,[14] although we have not found this to be the case.[15] Neither have we found a change in acetylcholinesterase that would account for resistance. Other potential mechanisms are under investigation.

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