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ASSESSING UNIT-PRICE RELATED REMIFENTANIL CHOICE IN RHESUS MONKEYS

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Given a commodity available at different prices, a unit-price account of choice predicts preference for the cheaper alternative. This experiment determined if rhesus monkeys preferred remifentanil (an ultra-short-acting μ-opioid agonist) delivered at a lower unit price over a higher-priced remifentanil alternative (Phases 1 and 3). Choice between equal-priced alternatives also was assessed (Phase 2). A discrete-trials procedure was arranged in which three monkeys chose between two remifentanil alternatives by responding on one of two levers. Different prices were arranged by manipulating drug dose (0.3 and 0.1 μg/kg/injection) and/or the ratio requirement. Monkeys usually chose the larger-dose alternative even when it was more expensive. Only when unit prices were relatively high (e.g., large response requirements) did monkeys choose the cheaper (or equally priced) smaller-dose alternative. Employing larger doses (0.9 and 0.3 μg/kg/injection) attenuated the larger-dose preference. The results demonstrate that choice was not determined simply by unit price. An alternative model that employs demand-function analysis to generate choice predictions is proposed.

Key words: Choice, unit price, remifentanil, drug self-administration, behavioral economics, lever press, rhesus monkey

On fixed-ratio (FR) schedules of reinforcement, the *unit-price* concept of behavioral economics may help understand choice of a single drug available at different doses and response requirements. Unit price is defined as a ratio of costs over benefits (e.g., Hursh, Raslear, Shurtleff, Bauman, & Simmons, 1988) in which cost variables are represented by the FR requirement and benefits are associated with the reinforcer magnitude or dose (Bickel, DeGrandpre, Higgins, & Hughes, 1990; Hursh, 2000). The unit price of a drug reinforcer can be expressed as:

$$\text{Unit Price} = \text{FR}/\text{Dose}. \quad (1)$$

Note that the unit price of a drug can be manipulated by changing the FR, the dose, or both.

Given a choice between a single commodity available at different unit prices, the lower-priced alternative should be chosen exclusively (Becker, 1971; Samuelson & Nordhaus, 1985). This hypothesis generally has been confirmed in studies using appetitive reinforcers (Green, Rachlin, & Hanson, 1983; Herrnstein & Loveland, 1975; Neuringer, 1967). Studies investigating choice of a drug at different doses, but at the same FR requirement, have shown near-exclusive choice of a larger (and cheaper) dose of cocaine, methylphenidate (Johanson & Schuster, 1975), or ethanol (Stewart, Wang, Bass, & Meisch, 2002) over a smaller dose of the same drug. In these studies, however, it is not clear if choice was determined by unit price or by dose. For example, would subjects choose the smaller-dose alternative if it was the cheaper alternative?

Madden, Bickel, and Jacobs (2000) investigated human smokers' choice of cigarette puffs available at a range of unit prices. Whereas subjects typically chose the lower-priced alternative, in some comparisons subjects chose the alternative associated with the larger number of cigarette puffs even though it was slightly more expensive than the smaller-puff alternative. When unit prices were equal,

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subjects usually preferred a larger number of puffs available at a larger FR over the smaller-puff alternative available at a smaller FR. Interestingly, at extremely high prices (arranged by increasing the FR of both alternatives) subjects reversed preference and selected the smaller-puff (and smaller-FR) alternative.

Anderson and Woolverton (2003) obtained similar results in a self-control procedure investigating cocaine choice in rhesus monkeys. Monkeys demonstrated near-exclusive choice for the larger dose of cocaine (0.1 mg/kg/inj) delayed by 30 s over a smaller dose (0.03 mg/kg/inj) delayed by 10 s. Although Anderson and Woolverton did not present their results within an economic framework, note that if delay is used as the cost variable then the two alternatives were equally priced. At longer delays (810 vs. 270 s) a preference reversal was obtained; monkeys chose the alternative associated with the smaller dose and shorter delay. The results of these two studies suggest that choice is more determined by drug dose at lower prices and by the response requirement (or delay) at higher prices.

Unit-price predictions of choice have not been assessed using opioid reinforcers. In the present study, we investigated choice in rhesus monkeys trained to self-administer remifentanil, an ultra-short-acting μ-opioid agonist useful in surgical procedures (Glass, Gan, & Howell, 1999; Rosow, 1999). Previous research in our laboratory has demonstrated that the reinforcing functions of remifentanil are similar to those of the longer-acting opioids alfentanil and fentanyl (Ko, Terner, Hursh, Woods, & Winger, 2002). We chose to use remifentanil to minimize drug accumulation across choice opportunities. We selected an intertrial interval (ITI) of 60 s because pilot work demonstrated that doses of 0.1 and 0.3 μg/kg/inj (used in the majority of this study) maintained similar response rates at an FR 10 (i.e., there were no rate-suppressing effects of the larger dose).

There were two major purposes of the research. First, we wanted to ascertain if predictions based on unit price could accurately account for rhesus monkeys' choice of remifentanil available at different doses and FR requirements. Second, we wanted to examine remifentanil choice when the two alternatives were equally priced but composed of different FR and dose combinations. We investigated remifentanil choice across a range of unit prices in Phase 1. Several comparisons dissociated choice predictions based on drug dose from predictions based on unit price. In Phase 2, we investigated choice between equally priced alternatives. In Phase 3, the unit price of the smaller-dose alternative was held constant and the unit price of the larger-dose alternative was progressively increased.

METHODS

Subjects

The subjects were 3 adult rhesus monkeys (*Macaca mulatta*), 2 male (Monkeys 3572 and 3603) and 1 female (Monkey 3600), with a history of drug self-administration including remifentanil. Monkeys lived in the experimental chambers and were fed 10 to 15 Purina monkey chow biscuits twice daily (at least 1.5 hr before experimental sessions) to maintain their body weights. Daily fresh fruit and other treats supplemented this diet. Water was continuously available. In accordance with institutional animal care and use requirements, environmental enrichment toys also were provided on a regular rotating basis.

Apparatus

Monkeys were permanently housed in stainless steel cages (83.3-cm long by 76.2-cm wide by 91.4-cm deep). The front, top, and bottom of the cage were made of barred stainless steel, and a pan was located below the floor to collect waste. Located on the wall to the left of the barred front door was an intelligence panel 20 cm in length and 15.4 cm in height, approximately 10 cm from the front and 19 cm from the bottom of the cage. Across the top of the stimulus panel, 1.5 cm apart, were three circular openings, 2.5 cm in diameter, covered with translucent plastic and capable of being illuminated from behind with 5-W colored bulbs. The two side lights could be illuminated red and the center light green. Centered below the right and left stimulus lights were response levers (Model 121-07, BRS-LVE) capable of being operated by 10 to 15 g (0.10–0.15 N) of force. A 0.3-cm thick stainless steel divider, centered between the response levers and below the stimulus lights,

extended 8 cm into the chamber. Experimental control was provided by an IBM PS/2 computer located in an adjoining room and programmed with Med-PC (Med-Associates, Georgia, VT) software.

Each monkey wore a Teflon mesh jacket (Lomir, Quebec, Canada) connected to a flexible stainless-steel spring tether attached to the rear of the cage. Monkeys had been implanted previously with indwelling intravenous catheters in an internal or external jugular, or femoral vein, under ketamine (10 mg/kg, IM) and xylazine (2 mg/kg, IM) anesthesia. Catheters were run subcutaneously from the site of implantation to an exit site in the middle of the back. Tubing was then fed through the steel spring tether and passed to the outside rear of the cage where it was connected to a stock solution of remifentanil (either 0.4 μg/kg/ml or 1.2 μg/kg/ml) and additional infusion lines that passed through the rollers of two infusion pumps. Different doses were arranged by manipulating the speed of the two pumps. Operation of one pump delivered 0.15 ml solution per s. Operation of the other delivered 0.05 ml solution per s. Injections were always 5 s in duration. When the stock solution was 0.4 μg/kg/ml remifentanil, operation of the faster pump resulted in a delivery of 0.3 μg/kg/inj (0.4 μg/kg/ml × 0.15 ml/s × 5 s) and operation of the slower pump delivered 0.1 μg/kg/inj. When the stock solution was prepared at 1.2 μg/kg/ml, doses of 0.9 and 0.3 μg/kg/inj were arranged.

General Procedure

Two sessions were conducted each day, one beginning at 10 a.m. and the other beginning at 4 p.m. The onset of stimulus lights signaled the beginning of the session and all stimulus lights were turned off at the end of the session. A discrete-trials procedure was employed. Sessions lasted until 60 trials had been completed or 2 hr had elapsed, whichever came first.

At the start of each trial the stimulus lights above the two levers were illuminated red. One press on either lever (choice) turned off both red lights for 0.5 s, following which the light above the selected lever was re-illuminated red. Completion of an FR on the selected lever resulted in a 5-s injection of remifentanil. During injections, the red light above the selected lever was turned off and the center light was illuminated green. Trials were separated by a 60-s ITI during which all stimulus lights were turned off.

We will refer to the FR requirements and doses associated with the two alternatives as a comparison. For example, one comparison consisted of choice between 0.3 μg/kg/inj (FR 30; left lever) and 0.1 μg/kg/inj (FR 30; right lever). When monkeys chose one alternative on greater than 90% of the trials, the consequences of responding on the two levers were reversed. We usually conducted two to five lever reversals in each comparison. In a few cases where monkeys did not exhibit a nearly exclusive preference for one alternative, lever reversals were not conducted because monkeys sampled both alternatives. Rather, comparisons were conducted for a minimum of 10 sessions and until obtained choice proportions were judged to be stable using a visual criterion of no consistent session-to-session trend.

The comparisons are grouped into three phases. The phases were not conducted sequentially, although most comparisons in Phase 1 were conducted prior to Phases 2 and 3. Some comparisons were replicated to assess for possible order effects. Table 1 shows the comparisons comprising each phase, the order in which they were conducted, and the FR, dose, and resulting unit price of each alternative. In comparisons investigating two different doses, also shown is the relative price (unit price of the larger-dose alternative divided by the unit price of the smaller-dose alternative).

Phase 1: Choice between Alternatives across Unit Prices

The purpose of Phase 1 was three-fold. First, we determined if the monkeys would select the larger dose of remifentanil (0.3 μg/kg/inj) over the smaller dose (0.1 μg/kg/inj) when both were available according to the same FR (Comparisons 1 and 2). Second, we determined if the monkeys would choose the smaller-FR alternative when both alternatives produced 0.1 μg/kg/inj (Comparison 3). This comparison also assessed if the smaller-dose alternative functioned as a reinforcer. Third, we assessed choice across a range of unit prices. In some comparisons the larger-dose alternative was cheaper (Comparisons 1, 2, and 4). The smaller-dose alternative was cheaper in others (Comparisons 5, 6, and 7).

Table 1

Order and description of each comparison. For each comparison the FR requirement, dose, and resulting unit price of each alternative are shown. Also shown is the relative price (larger-dose alternative / smaller-dose alternative). Absolute prices (and relative prices in Phase 3) have been rounded to the nearest whole number.

		Order			*Alt. 1*		*Alt. 2*		*Unit price*		*Price*
Phase	*Comp.*	*3572*	*3600*	*3603*	*FR*	*Dose*	*FR*	*Dose*	*Alt. 1*	*Alt. 2*	(L/S)
1	1	1	1	1	30	0.3	30	0.1	100	300	0.3
	2	6	7	7	100	0.3	100	0.1	333	1000	0.3
	3	2	4	4	10	0.1	30	0.1	100	300	
	4	4	5	2	10	0.3	30	0.1	33	300	0.1
	5	3	6	6	30	0.1	100	0.3	300	333	1.1
	6	22	29	31	30	0.1	200	0.3	300	667	2.2
	7	5	2	3	30	0.1	300	0.3	300	1000	3.3
	8	7	3	5	100	0.1	300	0.3	1000	1000	1
2	9	12	31	14	2	0.1	6	0.3	20	20	1
	10	9	32	9	4	0.1	12	0.3	40	40	1
	11	19	33	12	8	0.1	24	0.3	80	80	1
	12	8	34	8	16	0.1	48	0.3	160	160	1
	13	20,32	35	10	32	0.1	96	0.3	320	320	1
	14	21	36	13	64	0.1	192	0.3	640	640	1
	15	10	8,37	11	128	0.1	384	0.3	1280	1280	1
	16	11	14		256	0.1	768	0.3	2560	2560	1
	17	28	21	25	2	0.3	6	0.9	7	7	1
	18		16	23	4	0.3	12	0.9	13	13	1
	19	31	15	22	16	0.3	48	0.9	53	53	1
	20	29	17	24	32	0.3	96	0.9	107	107	1
	21	30	18		64	0.3	192	0.9	213	213	1
	22		19		128	0.3	384	0.9	427	427	1
	23		20		256	0.3	768	0.9	853	853	1
3	24	13	38	15	2	0.1	12	0.3	20	40	2
	25	14	39	16	2	0.1	18	0.3	20	60	3
	26	15	40	17	2	0.1	24	0.3	20	80	4
	27	16,33	9	18	2	0.1	30	0.3	20	100	5
	28	17,34	10,41	19	2	0.1	60	0.3	20	200	10
	29	18,35	11,30	20	2	0.1	120	0.3	20	400	20
	30	36	12,42	21	2	0.1	240	0.3	20	800	40
	31	37	13,43		2	0.1	480	0.3	20	1600	80
	32	27	22	26	2	0.3	12	0.9	7	13	2
	33		23	27	2	0.3	18	0.9	7	20	3
	34	26	24	28	2	0.3	24	0.9	7	27	4
	35	25	25	29	2	0.3	30	0.9	7	33	5
	36	24	26	30	2	0.3	60	0.9	7	67	10
	37	23	27		2	0.3	120	0.9	7	133	20
	38		28		2	0.3	240	0.9	7	267	40

In Comparison 8, the alternatives were equally priced. Comparison 6 was one of the last comparisons investigated in the experiment, conducted after Phases 2 and 3.

Phase 2: Choice between Equally Priced Alternatives

Table 1 also shows the 15 comparisons comprising Phase 2; the alternatives in each comparison were equally priced. In Comparisons 9-16, doses of 0.3 and 0.1 μg/kg/inj remifentanil were employed. Comparisons 17-23, conducted after exposure to Phase 3, assessed choice between 0.9 and 0.3 μg/kg/inj. The comparisons are numbered in order of ascending FR. Comparisons were not conducted in systematic order. We stopped increasing the FR when monkeys reliably chose the smaller-dose alternative or exhibited no preference. For Monkey 3603, we generally conducted more determinations per comparison (three to seven). This monkey experienced these comparisons first and we wanted to assess the consistency of preference across multiple lever reversals. Monkey 3600 initially was exposed to Comparison 15. When we increased the FR (Comparison 16), respond-

ing was not maintained; these data are not included in the results. This monkey then experienced comparisons in Phase 3 before returning to Phase 2, where responding was maintained in Comparison 16. For Monkeys 3572 and 3600, some comparisons using the smaller doses were conducted or replicated after exposure to the larger doses to assess for possible order effects.

Phase 3: Choice between a Constant-Priced Smaller-Dose Alternative and an Escalating-Priced Larger-Dose Alternative

In Phase 3, the smaller-dose alternative always was available according to an FR 2. We increased the FR associated with the larger-dose alternative as follows: 12, 18, 24, 30, 60, 120, 240, 480. Not all monkeys experienced all comparisons. Comparisons usually were conducted in ascending order (the most notable exceptions are Comparisons 32-37, which were conducted in descending order for Monkey 3572), and we stopped increasing the FR associated with the larger-dose alternative when monkeys reliably chose the smaller-dose alternative. Table 1 also shows the 15 comparisons comprising Phase 3. In Comparisons 24-31, choice between 0.3 and 0.1 μg/kg/inj remifentanil was investigated. Comparisons 32-38 investigated choice between 0.9 and 0.3 μg/kg/inj and mostly were conducted after comparisons investigating the smaller doses. For Monkeys 3572 and 3600, some comparisons using the smaller doses were conducted or replicated after exposure to the larger doses. Monkey 3603 received only one determination in Component 28; this was an oversight.

RESULTS

For each comparison, the total number of determinations (the initial exposure plus lever reversals, including replicated comparisons) conducted, the mean number of sessions required for near-exclusive choice to develop, and the mean response rate (resp/s) for each comparison are shown in the Appendix. Response rates are based on the final session in each determination, collapsed across lever reversals, and were calculated using the time to complete the FR after an alternative was selected. Unfortunately, trial-by-trial latencies to select an alternative were not collected. Unless otherwise noted, subsequent analyses of choice are based on the final session in each determination (where one alternative was chosen on >= 90% of the trials), collapsed across lever reversals.

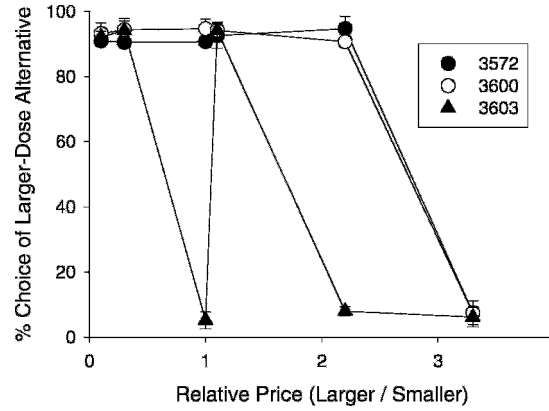

Fig. 1. *Phase 1.* Mean percent choice (and standard deviation) of the larger-dose alternative as a function of relative price (unit price of the larger-dose alternative/unit price of the smaller-dose alternative).

Phase 1

All monkeys developed near-exclusive choice of the larger-dose alternative when the comparison differed only in terms of drug dose (Comparisons 1 and 2), although Monkey 3572 required more sessions before near-exclusive choice developed in Comparison 1. Monkeys also developed near-exclusive choice of the smaller-FR alternative when dose was held constant (Comparison 3). The fact that responding was maintained in Comparison 3 demonstrates that 0.1 μg/kg/inj functioned as a reinforcer. The number of trials completed was determined by the FR associated with the selected alternative and was not dose dependent. When the FR was 100 or less, monkeys usually completed all 60 trials. At larger FR requirements, monkeys usually completed between 40 and 50 trials.

Figure 1 shows the mean percent choice of the larger-dose alternative across all comparisons in Phase 1 (excluding Comparison 3, in which only the smaller dose was available). Choice is plotted as a function of the relative price of the larger-dose alternative (unit price of the larger-dose alternative / unit price of the smaller-dose alternative). Results have been collapsed across Comparisons 1 and 2 because relative price is identical. Error bars represent standard deviations.

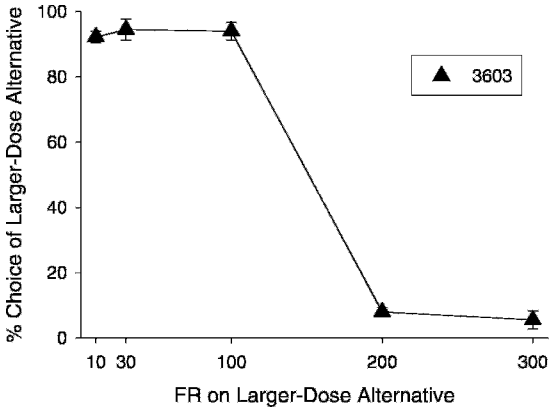

Fig. 2. *Phase 1 (Monkey 3603).* Mean percent choice (and standard deviation) of the larger-dose alternative as a function of the response-requirement associated with it.

Monkeys 3572 and 3600 preferred the larger-dose alternative in all but one comparison, even when it was more expensive. Only in Comparison 7 (where the larger-dose alternative was 3.3 times that of the unit price for the smaller-dose alternative) were these monkeys sensitive to differences in unit price.

Monkey 3603 selected the lower unit priced alternative in all comparisons except Comparison 5 where the smallest programmed difference in unit prices was arranged. Although this suggests that this monkey preferred the cheaper alternative, the fact that in Comparison 8 (equal unit prices) the smaller-dose alternative was strongly preferred suggests that this monkey simply avoided large FR requirements. As shown in Figure 2, this monkey chose the larger-dose alternative only when it was available at FR 100 or less.

Phase 1 arranged one comparison in which the two alternatives were equally priced (Comparison 8). In addition, the prices were almost identical in Comparison 5. All the monkeys preferred the larger-dose alternative in Comparison 5, and two of the three monkeys preferred the larger-dose alternative in Comparison 8. Phase 2 provides a parametric investigation of choice when the two alternatives were equally priced.

Phase 2

Figure 3 shows the mean percent choice of the larger-dose alternative as a function of the FR programmed on that alternative in Phase 2;

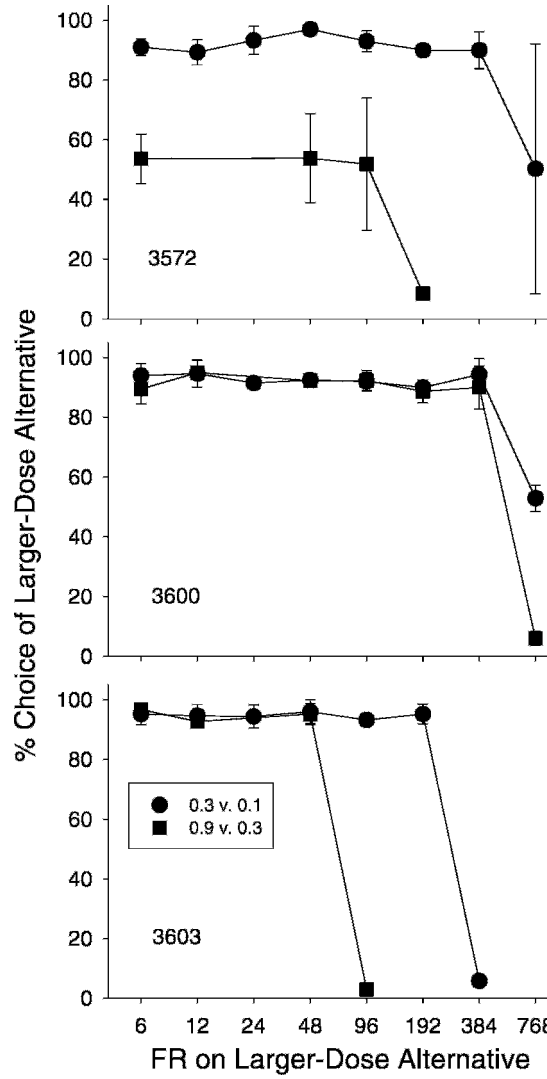

Fig. 3. *Phase 2.* Mean percent choice (and standard deviation) of the larger-dose alternative as a function of the FR programmed on that alternative. The response requirement associated with the smaller-dose alternative was one-third that of the larger-dose alternative. Circles represent comparisons employing 0.3 and 0.1 µg/kg/inj. Squares represent comparisons employing 0.9 and 0.3 µg/kg/inj.

the smaller-dose FR value was always was one-third that of the larger-dose. All three monkeys demonstrated near-exclusive choice of the larger dose across a range of increasing FR requirements. With respect to comparisons investigating choice between 0.3 and 0.1 µg/kg/inj (circles), Monkey 3572 developed a lever bias at FR 256/768 (Comparison 16), selecting the left lever regardless of the

alternative associated with it. Monkey 3600 chose both alternatives about equally at FR 256/768. For this monkey, when we increased the FR requirements further, responding was not maintained and these data are not reported. Monkey 3603 chose the smaller-dose alternative at FR 128/384. We will term the switch from selecting the larger-dose alternative to selecting the smaller-dose alternative as a preference reversal.

When larger doses were investigated (Figure 3, squares), Monkeys 3600 and 3603 continued to choose the larger-dose alternative (0.9 μg/kg/inj) across a range of increasing ratios. At greater FR requirements, a preference reversal was obtained for these monkeys. Monkey 3572 was indifferent across a wide range of FR values, though preference for the smaller-dose alternative was observed at FR 64/192. For all monkeys, preference for the smaller-dose alternative emerged at smaller ratio values relative to choices between 0.3 and 0.1 μg/kg/inj.

Figure 4 shows the mean number of trials completed as a function of the FR programmed on the larger-dose alternative. Open symbols represent comparisons in which the smaller-dose alternative was preferred, or comparisons in which neither alternative was preferred.

With respect to choice between 0.3 and 0.1 μg/kg/inj (circles), the monkeys completed all 60 trials at smaller response requirements. Subsequently, the number of trials completed decreased as a function of the FR. When Monkey 3603 reversed preference and selected the smaller-dose alternative, the number of trials completed increased. Monkeys 3572 and 3600 did not reliably select either alternative at FR 256/768.

When larger doses were investigated (squares), the monkeys completed 50-60 trials at the smallest FR. Trials completed decreased at smaller ratios relative to comparisons investigating choice between 0.3 and 0.1 μg/kg/inj. Trials completed increased when the monkeys reversed preference and selected the smaller-dose alternative. These results suggest that 0.9 μg/kg/inj remifentanil suppressed responding.

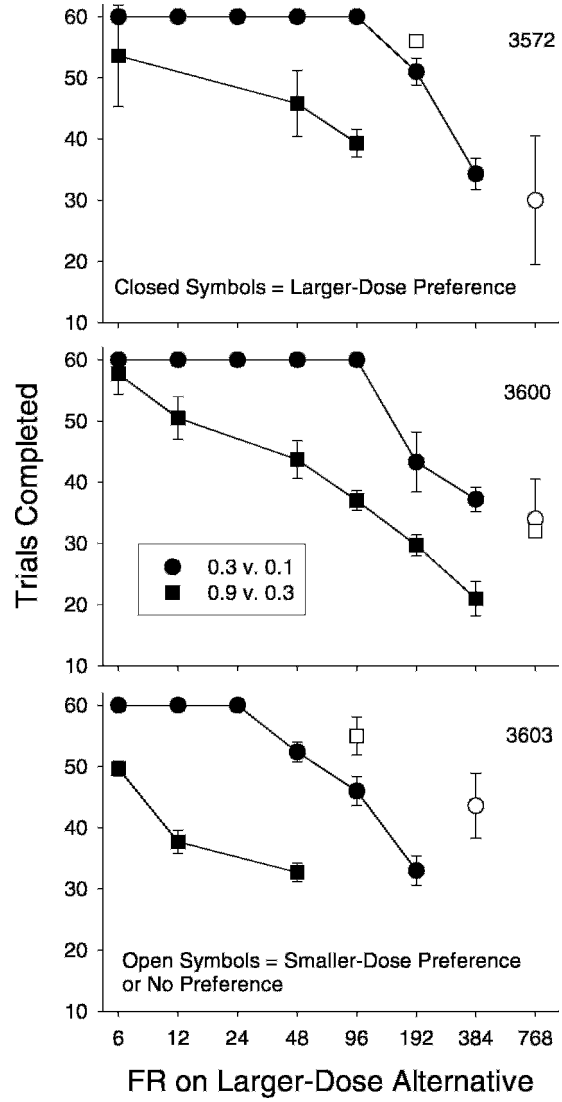

Fig. 4. *Phase 2.* Mean number of trials completed as a function of the response requirement programmed on the larger-dose alternative. Error bars represent standard deviations. Circles represent comparisons employing 0.3 and 0.1 μg/kg/inj; squares represent comparisons employing 0.9 and 0.3 μg/kg/inj. Open symbols represent comparisons in which the larger-dose alternative was not preferred.

Phase 3

In Phase 3 the smaller-dose alternative always was available according to an FR 2 and the unit price of the larger dose always exceeded that of the lower-dose alternative. Figure 5 shows the mean percent choice of the larger-dose alternative as a function of its FR requirement. Results from Comparisons 9 and 17 of Phase 2 also are shown because the smaller-dose was available on an FR 2.

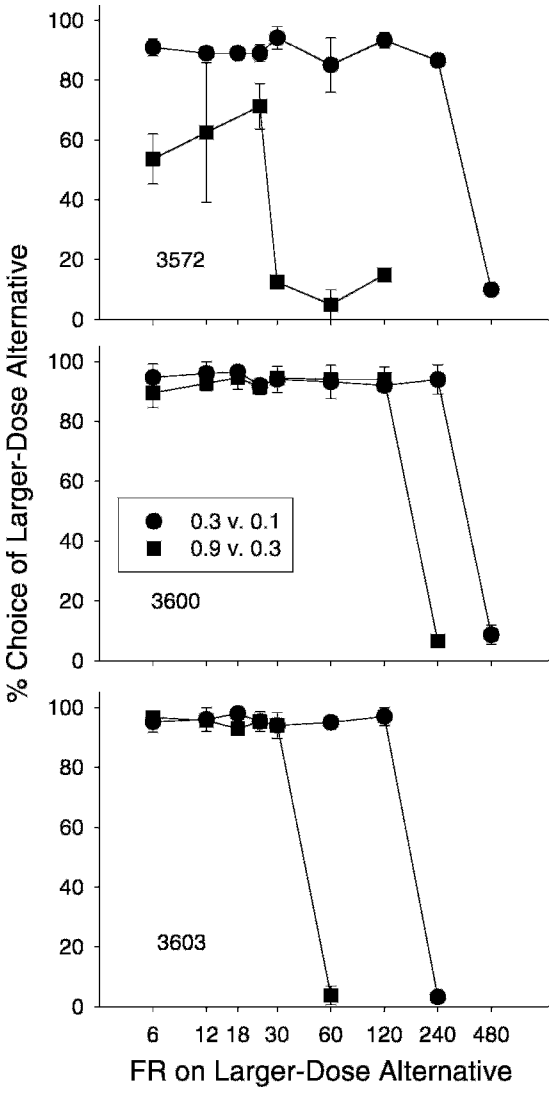

Fig. 5. *Phase 3.* Mean percent choice (and standard deviation) of the larger-dose alternative as a function of its programmed response requirement. The response requirement associated with the smaller-dose alternative was held constant at an FR 2.

In the smaller dose pairing (0.3 v. 0.1; circles) all the monkeys selected the larger-dose alternative more frequently despite its being the higher-priced alternative. Monkeys 3572 and 3600 selected the larger dose nearly exclusively even when its price was 40 times that of the smaller-dose alternative, whereas Monkey 3603 preferred the larger dose when it was 20 times more expensive than the smaller-dose alternative (Table 1). At larger FR values (FR 240 and 480), preference reversed to the smaller-dose alternative.

The squares in Figure 5 represent choice between doses of 0.9 and 0.3 μg/kg/inj. Again, Monkeys 3600 and 3603 preferred the larger-dose, more expensive alternative, but a preference reversal occurred at lower ratios (FR 240 and 60, respectively) relative to the smaller doses. Similar to the results obtained in Phase 2 with larger doses, Monkey 3572 did not exhibit a consistent dose preference across the FR 6–24 range. This monkey reliably selected the smaller-dose alternative when the larger-dose alternative produced drug according to an FR 30 schedule and thereafter.

Figure 6 shows the mean number of trials completed as a function of the FR programmed on the larger-dose alternative. In the smaller-dose pairing (circles) the monkeys completed all 60 trials across a range of increasing FR requirements. Trials completed decreased at larger FR requirements. When larger doses were employed, trials completed decreased at lower ratios relative to the smaller doses. When monkeys selected the smaller-dose alternative (available according to an FR 2), they completed all (or almost all) 60 trials.

As shown in Figures 3 and 5 (Phases 2 and 3), Monkey 3572 never strongly preferred the larger-dose alternative in the larger-dose pairing (0.9 and 0.3 μg/kg/inj). In light of these results, we wanted to determine if this monkey would reliably choose the larger- over the smaller-dose alternative when both were available at FR 30. As before, this monkey did not reliable select the larger-dose alternative, suggesting problems with dose discrimination in the larger-dose pairing for this monkey.

DISCUSSION

According to unit-price predictions of choice, when the same commodity is available at different prices on FR schedules, exclusive choice should develop for the cheaper alternative. The results obtained using the μ-opiod agonist remifentanil do not support this hypothesis. Across a wide range of prices, monkeys almost always chose the larger-dose alternative, even if it was the more expensive alternative. This effect can be seen most dramatically in Figure 5 (0.3 vs. 0.1 μg/kg/inj), where monkeys preferred the larger-dose alternative available at an FR 120 or

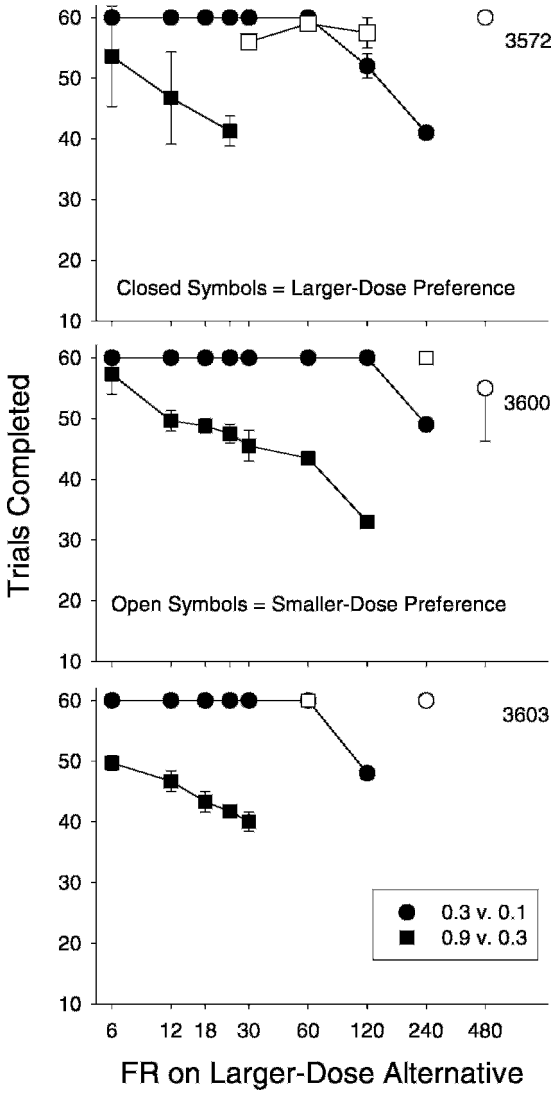

Fig. 6. *Phase 3.* Mean number of trials completed as a function of the response requirement programmed on the larger-dose alternative. See Figure 4 for more details.

240 over the smaller-dose alternative available at an FR 2.

Madden et al. (2000) reported that at relatively low unit prices, human smokers preferred a larger number of cigarette puffs over a smaller number of puffs, even if the larger-puff alternative was the slightly more expensive alternative. At relatively high unit prices, a preference reversal occurred and subjects chose the smaller-puff alternative. The results obtained in the present study are consistent with these results. Our results also are consistent with those reported by Anderson and Woolverton (2003) in which rhesus monkeys preferred a more delayed but larger dose of cocaine over a more immediate smaller dose across a range of delays. Interestingly, in both our study and Anderson and Woolverton's, employing larger overall doses of drug attenuated the larger-dose preference. These results are inconsistent, however, with findings obtained by Foster and Hackenberg (2004), who investigated pigeons' choice between food alternatives available at different FR requirements but equal unit prices. Preference for the smaller-magnitude reinforcer available at a smaller response requirement was obtained. This discrepancy may reflect procedural differences, species differences, or differences between reinforcers (food versus drug).

Madden et al. (2000) sought to account for systematic deviations from a strict unit-price interpretation of choice by expanding the unit-price equation to include the handling costs associated with reinforcer consumption (e.g., removing the cigarette, lighting it, placing it into a plastic holder, etc.) and the obtained delay to reinforcement. Madden et al. postulated that the value of the reinforcer (V) is degraded according to Mazur's (1984) hyperbolic discounting function. Incorporating the discounted value of the reinforcer and associated handling costs (H), Madden et al. reported that a modified unit-price equation,

$$\text{Unit Price} = (\text{FR} + \text{H})/\text{V}, \qquad (2)$$

was somewhat accurate in predicting choice. In Madden et al.'s study, the handling costs were the same regardless of whether the larger- or smaller-puff alternative was selected. Therefore the relative handling costs (handling costs per puff) were greater for the smaller-puff alternative. At low prices (and brief delays) differences in handling costs resulted in preference for the larger-puff alternative. At high prices (and longer delays) the handling costs relative to the costs associated with the increasing FR became minimal. Additionally, the value of the more-delayed larger-puff alternative was sufficiently degraded to result in preference for the smaller-puff alternative.

Although our main findings are similar to those obtained by Madden et al. (2000), they

cannot be predicted by this modified unit-price equation. First, there were no handling costs in our experiment because intravenous drug delivery does not require a consummatory response. Second, although degrading the value of the (more delayed) larger-dose alternative may result in a preference reversal, it cannot account for the preference for the more expensive larger-dose alternative, particularly in Phase 3. Degrading the value of the larger-dose alternative by incorporating delay as a cost variable would only increase the cost of the already more expensive (yet preferred) larger-dose alternative.

There are several possible reasons why our results are inconsistent with unit-price predictions of choice. Demand-function analysis has shown that for some drugs (e.g., cocaine) the smallest reinforcing dose is more elastic than larger doses (Hursh & Winger, 1995). Although Hursh and Winger demonstrated that this is not the case with remifentanil, they employed a 10-s timeout following drug delivery whereas we used a 60-s ITI. To the extent that drug accumulation is necessary for scalar equivalence to exist between drug doses, perhaps our use of the ultra-short acting opioid combined with a long ITI contributed to the larger-dose preference.

Constraints imposed by the use of a discrete-trials procedure also could have contributed to the larger-dose preference. In Madden et al.'s (2000) study, sessions were time-based. Smokers could earn the same total number of puffs by selecting the larger-puff alternative or selecting the smaller-puff alternative and completing more ratios. In our study, the same level of remifentanil consumption could not be maintained by selecting the smaller-dose alternative and completing three times as many trials (there was a 60-trial limit). Choosing the larger-dose alternative, then, was the only way to defend consumption against increasing FR requirements. Perhaps monkeys preferred the larger-dose alternative (even if it was more expensive) at prices where remifentanil demand was inelastic and total consumption could be defended.

The demand function in Figure 7 shows remifentanil consumption plotted as a function of unit price. These results were obtained from a previous study in our laboratory that investigated doses of 0.03, 0.1, and 0.3 μg/kg/inj (Ko et al., 2002). The dashed lines indicate

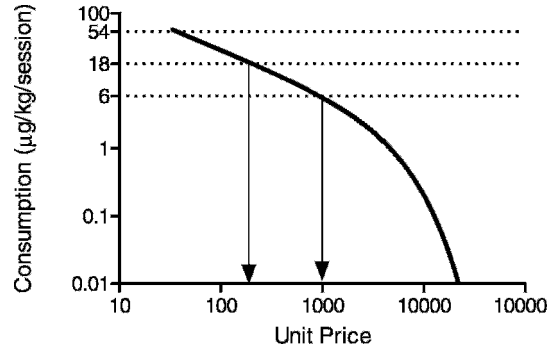

Fig. 7. Remifentanil consumption as a function of unit price. The results are from those reported by Ko et al.(2002). Superimposed on this demand function are the consumption constraints imposed by the present procedure. Each dashed line shows the total consumption for exclusive choice of 0.1, 0.3, and 0.9 μg/kg/inj. The arrows represent the hypothetical point at which choosing either dose alternative results in equivalent total consumption.

the consumption limitations imposed by the current experiment. For example, if 0.3 μg/kg/inj was selected on all 60 trials, total consumption would equal 18 μg/kg/session. Note that this amount is substantially less than the remifentanil consumed at low prices in a fixed 2-hr session in the experiment by Ko et al. We hypothesize that across a range of prices, monkeys defended this (already constrained) level of consumption by choosing the larger-dose alternative. At prices where remifentanil demand is elastic, consumption decreases (fewer trials are completed) and at some price consumption approaches a level (6 μg/kg/session) that could be obtained by near-exclusive choice of the smaller-dose alternative (shown by the arrow at a unit price of 1000). At this point the preference reversal may occur. Consistent with our results, Figure 7 shows that the preference reversal should occur at lower prices when larger doses are investigated (0.9 and 0.3 μg/kg/inj).

Superimposed on the demand function obtained by Ko et al.(2002), average session consumption from Phases 2 and 3 are presented in Figures 8 and 9. (The results obtained from Phase 1 are not easily conducive to this type of presentation because the unit prices associated with both alternatives varied simultaneously and disproportionately across comparisons.) Figure 8 shows the mean consumption as a function of unit price in Phase 2. Circles represent comparisons investigating

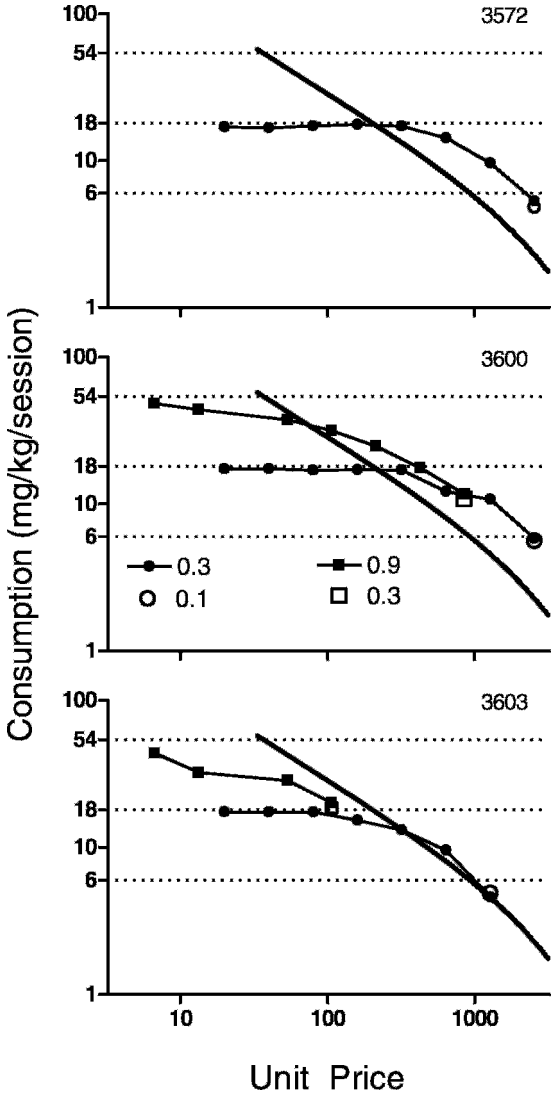

Fig. 8. Average total session consumption from each comparison in Phase 2, superimposed on the remifentanil demand function described in Figure 7. Each dashed line shows the total consumption for exclusive choice of 0.1, 0.3, and 0.9 μg/kg/inj remifentanil. Circles represent comparisons investigating choice between 0.3 and 0.1 μg/kg/inj; squares represent choice between 0.9 and 0.3 μg/kg/inj. Open symbols represent comparisons in which either the smaller-dose alternative was preferred or indifference was obtained. The last point on the closed function represents an estimate of the total session consumption in this comparison before preference for the smaller-dose alternative (or indifference) developed (see text for more details).

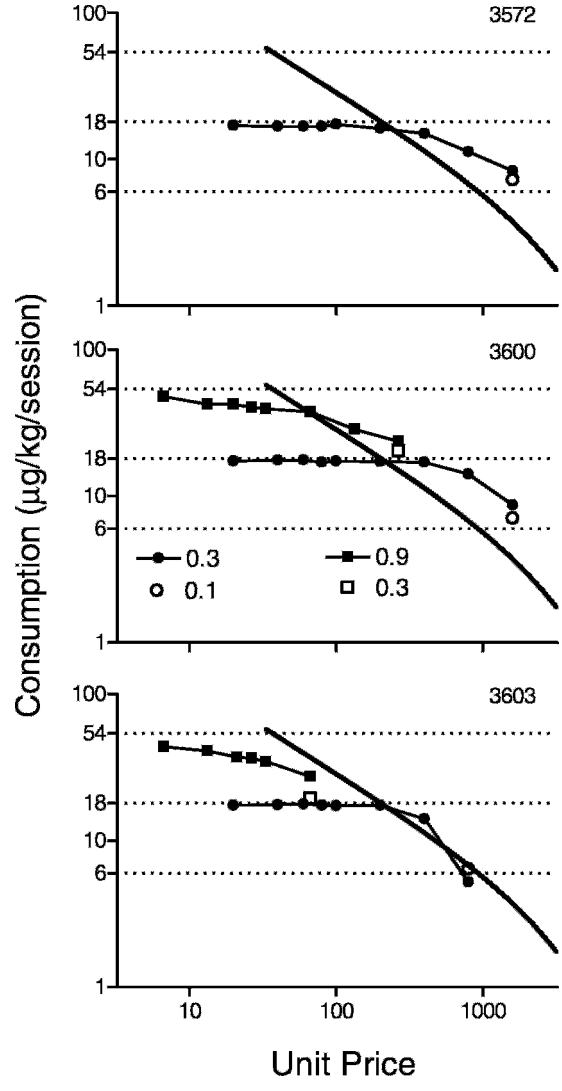

Fig. 9. Average daily consumption from each comparison in Phase 3. See Figure 8 for more details.

choice between 0.3 and 0.1 μg/kg/inj. Squares represent comparisons investigating the larger doses (results from Monkey 3572 have been omitted because this monkey did not reliably discriminate these doses). The functions with solid symbols represent comparisons in which the larger-dose alternative was preferred. The last point on these functions shows consumption in the comparison that ultimately produced the preference reversal before near-exclusive preference for the smaller-dose alternative developed. In most cases this consumption measure came from one of the first sessions in the comparison when the larger-dose alternative was still preferred. This point is meant to serve only as an estimate of the total consumption if the larger-dose alternative had been chosen exclusively;

it probably overestimates consumption because it includes intake from additional smaller-dose deliveries. Average consumption when the smaller-dose alternative was preferred is shown by the open symbols. There were two exceptions to these calculations, both involving choice between 0.3 and 0.1 μg/kg/inj at the points corresponding to the preference reversal. Monkey 3600 responded on both levers in this comparison, and choice proportions approximated 0.5. We calculated consumption during the session in which this monkey selected the larger-dose alternative the most times (closed circle) and the session in which the smaller-dose alternative was selected the most times (open circle). Monkey 3572 developed a near-exclusive preference for the left lever. When left-lever pressing produced the larger-dose alternative, consumption is shown by the closed circle, and when the smaller-dose alternative, by the open circle.

With respect to choice between the smaller doses (circles), the constraints imposed by the discrete-trials procedure resulted in markedly lower consumption relative to that obtained by Ko et al. (2002). Across a range of prices, all monkeys consumed slightly less than 18 μg/kg/session. Consumption decreased with further increases in price. For Monkey 3603, consumption on the elastic portion of the function was similar to that obtained by Ko et al. For the other two monkeys, remifentanil demand was more inelastic than that obtained by Ko et al. These differences could be attributed to differences in the doses of remifentanil assessed, differences in the duration of the timeout (or ITI) following the drug injection, or simply may reflect differences among individual monkeys.

Of critical importance is the total consumption at the point where the larger-dose alternative was no longer preferred. Near-exclusive choice of the smaller-dose alternative resulted in a similar level of consumption relative to the estimated consumption had the larger-dose alternative been selected. The same finding was obtained when larger doses were employed, and the point at which obtained consumption was almost identical regardless of dose selected occurred at lower overall prices.

Figure 9 shows the average session consumption from Phase 3 plotted as a function of the unit price of the larger-dose alternative. Overall, the results are similar to those shown in Figure 8. At the point of the preference reversal, total consumption when the smaller-dose alternative was selected (open symbols) approximated the estimated consumption obtained when the larger-dose alternative was preferred.

The results from the larger-dose comparisons (squares) for Monkey 3603 represent the largest deviation from this general finding. This monkey selected the smaller-dose alternative (open square) when choice of the larger-dose alternative (closed square) would have produced more drug. These results must be interpreted cautiously because this monkey never actually preferred the larger-dose alternative in any session during this comparison (Comparison 36). The last closed square shows intake during the session in which the larger-dose alternative was chosen the most times. In this session, the larger-dose alternative was selected 11 times and the smaller-dose alternative was selected 49 times. Therefore, the consumption shown by the last closed square is not an accurate estimate of the total intake that would have been obtained if this monkey chose the larger-dose alternative exclusively.

Bickel, Marsch, and Carroll (2000) proposed that, under some circumstances, examining demand functions for two different commodities may yield accurate choice predictions. Our results suggest that demand functions may be useful in predicting choice between the same drug available at different prices. At prices where demand is inelastic, subjects preferred the larger-dose alternative, even if it was more expensive. The preference reversal occurred on the elastic portion of the demand function. Future research, in which demand functions for each dose are obtained prior to the choice situation, may determine if the preference reversal occurs at the point at which demand switches from inelastic to elastic, or the point at which choosing the more expensive larger-dose alternative does not result in increased total consumption relative to the smaller-dose alternative.

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APPENDIX

Total number of determinations conducted, the mean number of sessions (per determination) required for near-exclusive choice to develop, and the mean response rate (resp/s) for each comparison. Standard deviations are shown in parentheses. (See Table 1 for dose and FR response requirements used in each comparison.)

Phase	*Monkey*	*Comp.*	*Det.*	*Sessions*	*Resp/s*
1	3572	1	5	14.0 (5.3)	1.9 (1.8)
		2	4	3.2 (1.3)	2.6 (1.8)
		3	5	12.2 (5.9)	3.9 (1.3)
		4	3	8.0 (3.0)	3.4 (2.8)
		5	5	5.2 (1.2)	3.4 (1.8)
		6	3	2.7 (0.5)	2.6 (1.7)
		7	4	8.0 (8.7)	4.1 (1.9)
		8	4	10.5 (5.6)	2.9 (2.1)
	3600	1	5	2.2 (0.4)	3.7 (1.1)
		2	7	1.1 (0.3)	4.0 (0.7)
		3	6	7.0 (2.8)	4.6 (1.2)
		4	5	4.6 (1.5)	4.7 (0.9)
		5	6	1.7 (0.7)	4.3 (0.7)
		6	3	5.7 (4.5)	3.0 (1.2)
		7	5	5.8 (4.4)	3.7 (1.2)
		8	3	4.3 (3.3)	3.4 (1.0)
	3603	1	4	3.2 (1.9)	2.9 (0.9)
		2	5	1.2 (0.4)	2.6 (1.0)
		3	6	4.2 (4.4)	2.9 (0.9)
		4	4	1.7 (0.4)	3.1 (1.0)
		5	4	4.7 (3.3)	3.0 (1.0)
		6	3	1.7 (0.9)	2.1 (1.2)
		7	4	1.5 (0.5)	3.2 (0.8)
		8	6	1.8 (1.9)	2.3 (0.8)
2	3572	9	3	1.7 (0.5)	2.5 (1.9)
		10	3	9.3 (7.6)	2.8 (2.3)
		11	3	4.7 (1.2)	3.2 (2.6)
		12	3	3.0 (0.8)	2.9 (2.4)
		13	4	2.2 (0.8)	3.9 (1.9)
		14	3	2.0 (0.8)	3.0 (1.6)
		15	3	5.0 (3.2)	3.1 (1.6)
		16	3	7.3 (2.0)	3.5 (1.6)
		17	1	18.0 (0.0)	2.7 (2.6)
		19	2	10.0 (0.0)	2.2 (2.1)
		20	3	11.3 (1.2)	3.1 (1.7)
		21	2	5.0 (2.0)	3.2 (1.6)
	3600	9	2	3.5 (1.5)	3.3 (1.6)
		10	3	1.7 (0.9)	2.1 (1.4)
		11	2	3.0 (1.0)	2.5 (1.1)
		12	2	2.0 (1.0)	2.4 (1.3)
		13	2	1.0 (0.0)	2.7 (1.1)
		14	3	3.0 (0.8)	2.6 (1.3)
		15	6	7.2 (3.4)	3.3 (1.0)
		16	1	16.0 (0.0)	3.1 (1.0)
		17	4	5.5 (3.6)	2.2 (1.7)
		18	2	2.5 (0.5)	1.5 (1.6)
		19	3	3.3 (0.5)	1.4 (1.3)
		20	3	2.3 (1.9)	2.0 (1.4)
		21	3	2.0 (0.8)	2.4 (1.2)
		22	3	3.7 (2.5)	2.6 (0.8)
		23	3	5.3 (2.0)	3.3 (0.8)
	3603	9	5	1.4 (0.8)	2.8 (1.2)
		10	5	1.0 (0.0)	2.5 (1.0)
		11	5	1.2 (0.4)	2.8 (0.9)
		12	7	1.4 (1.0)	2.3 (0.8)
		13	5	1.2 (0.4)	2.5 (0.7)
		14	5	1.4 (0.8)	2.3 (0.8)

APPENDIX
(*Continued*)

Phase	*Monkey*	*Comp.*	*Det.*	*Sessions*	*Resp/s*
2	3603	15	5	2.6 (1.6)	2.5 (0.9)
		17	3	3.0 (2.8)	2.9 (1.3)
		18	4	2.5 (0.5)	2.5 (1.2)
		19	4	2.0 (1.0)	2.5 (0.9)
		20	4	1.2 (0.4)	2.6 (0.7)
3	3572	24	3	2.7 (0.9)	3.0 (2.3)
		25	2	3.5 (1.5)	3.2 (2.5)
		26	3	9.0 (5.7)	2.5 (2.4)
		27	4	4.2 (3.4)	2.3 (2.5)
		28	6	6.5 (5.0)	2.4 (2.1)
		29	4	2.2 (0.8)	3.2 (1.6)
		30	2	1.5 (0.5)	3.9 (1.6)
		31	2	4.5 (1.5)	8.6 (2.9)
		32	4	9.2 (4.9)	2.5 (3.0)
		34	1	14.0 (0.0)	2.0 (2.7)
		35	2	2.5 (0.5)	3.0 (3.3)
		36	2	8.0 (5.0)	2.9 (3.3)
		37	2	4.0 (3.0)	4.0 (3.6)
	3600	24	2	1.5 (0.5)	3.6 (1.6)
		25	2	1.0 (0.0)	3.5 (1.7)
		26	3	2.7 (1.7)	2.2 (1.6)
		27	3	2.0 (1.0)	3.9 (0.8)
		28	5	2.0 (1.2)	3.0 (1.3)
		29	6	2.2 (1.3)	2.9 (0.9)
		30	7	2.3 (2.2)	3.2 (0.9)
		31	6	2.0 (1.0)	5.9 (3.7)
		32	3	3.0 (2.2)	1.1 (1.2)
		33	5	2.0 (0.6)	1.4 (1.3)
		34	2	1.0 (0.0)	1.3 (1.0)
		35	2	2.5 (1.5)	1.3 (1.0)
		36	2	1.5 (1.5)	1.5 (1.0)
		37	3	6.0 (4.5)	1.9 (0.8)
		38	3	3.0 (0.0)	6.1 (3.9)
	3603	24	2	1.0 (0.0)	2.9 (1.1)
		25	2	1.0 (0.0)	3.1 (0.9)
		26	3	1.3 (0.5)	3.3 (0.9)
		27	2	1.0 (0.0)	3.2 (0.9)
		28	1	2.0 (0.0)	2.6 (0.8)
		29	2	1.0 (0.0)	2.8 (0.8)
		30	3	2.0 (0.0)	3.3 (2.9)
		32	3	1.0 (0.0)	3.0 (0.8)
		33	3	1.7 (0.5)	3.1 (0.9)
		34	3	1.0 (0.0)	2.7 (0.9)
		35	3	1.3 (0.5)	2.5 (0.8)
		36	5	2.5 (1.2)	4.4 (3.2)