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Reinforcing effectiveness of midazolam, ethanol, and sucrose: Behavioral economic comparison of a mixture relative to its component solutions

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Abstract

Benzodiazepines (BZs) are relatively safe when administered alone. However, these drugs can produce severe side effects when co-administered with ethanol. Despite these adverse consequences, rates of concurrent BZ and ethanol misuse are increasing, and it is unclear if this behavior is maintained by an enhanced reinforcing effect of the mixture. To address this issue, the current study compared the reinforcing effectiveness of sucrose solutions mixed with midazolam, ethanol, or both. Eight male rats were trained to orally self-administer solutions of either sucrose (S), sucrose + midazolam (SM), sucrose + ethanol (SE), or sucrose + midazolam + ethanol (SME). The response requirement was increased between sessions until the number of reinforcers earned was zero, and the relationship between response requirement and reinforcers earned was analyzed using the behavioral economic approach of exponential model of demand. Baseline intake was similar across drug conditions. Consumption of SM was least affected by increases in cost, indicating it possessed the highest reinforcing effectiveness (i.e., least elastic). The reinforcing effectiveness of S, SE, and SME did not differ significantly. The fact that the reinforcing effectiveness of the SME was less than that of SM does not support the supposition that BZ and ethanol co-administration is maintained by a higher reinforcing effectiveness of the mixture.

Keywords

Polydrug; self-administration; benzodiazepine; alcohol; rat

Introduction

Benzodiazepines (BZs) are commonly prescribed treatments for anxiety and sleep disorders, with approximately 5.2% of the United States population receiving a prescription in 2008 (Olfson et al., 2015). The popularity of these drugs is maintained, in part, by their perception as safe medications with low risk of toxicity (Mendelson et al., 1996; Roehrs and Roth, 2012; Werner and Covenas, 2014). However, the number of deaths related to BZs increased 5-fold from 1999-2009 in the United States (Calcaterra et al., 2013). This increase in BZ-related deaths was observed despite a relatively steady, if not decreasing, estimated prescribing rate over a similar time period (2001: 90 million; 2007: 85 million; 2008: 75 million), suggesting that these deaths were not the consequence of an increase in availability (Olfson et al., 2015; Rickels, 2013; Stahl, 2002). One possible explanation for the observed rise in BZ-related deaths could be an increase in the prevalence of co-administration with other sedatives such as opioids and/or ethanol, which can result more serious emergency department visits and death risk (SAMHSA DAWN Report 2014). BZ product labeling warns against ethanol co-administration, as the mixture has increased potency to produce respiratory depression, motor impairment, and death (Dorian et al., 1985; Hu et al., 1987; Linnoila et al., 1990; Maickel and Nash, 1986). However, rates of emergency department visits associated with BZs combined with ethanol continue to rise (Day, 2014), and the determinants of this potentially lethal drug-taking behavior remain unclear.

Previous reports have demonstrated that BZs can alter the abuse-related effects of several drugs of abuse. Interestingly, this effect tends to be bidirectional, with BZs enhancing the abuse-related effects of some drug classes, while diminishing these effects in others. For example, BZs have been reported to increase many of the abuse-related effects of opioids (Ator et al., 2005; Busto et al., 1996; Iguchi et al., 1993; Farre et al., 1998; Lintzeris et al., 2006; Preston et al., 1984; Spiga et al., 2001; Walker and Ettenberg, 2003), which is thought to contribute to the high incidence of their co-abuse (see Jones et al., 2012 for review). Conversely, BZs appear to reduce the abuse-related effects of psychostimulants (Augier et al., 2012; Barrett et al., 2005; Goeders et al., 2014; Lile et al., 2011; Marks et al., 2014; Weerts et al., 2005) commensurate with the seemingly low prevalence of their co-administration (but see Wolf et al., 2005).

Given the apparent prevalence of BZ and ethanol co-administration, one might expect BZs to increase the abuse-related effects of ethanol. Furthermore, both BZs and ethanol elicit similar effects at the GABA_A receptor through distinct binding sites (Caputo and Bernardi, 2010; Endoh et al., 2008; Jembrek and Vlainic, 2015), suggesting that BZs could augment the reinforcing effects of ethanol and vice versa (see Chester and Cunningham, 2002; Endoh et al., 2008; Koob et al., 2004 for review). However, investigations of this possibility have yielded seemingly equivocal findings, at least in terms of ethanol consumption. For instance, studies have reported that BZ treatment increases (Petry, 1995; Petry, 1997; Sawyer et al., 2014; Schmitt et al., 2002; Soderpalm and Hansen, 1998; Winger et al., 2007), decreases (Chan et al., 1983a,b; Roehrs et al., 1984; Samson and Grant, 1985), or has no effect (Barrett and Weinberg, 1975; Leonard et al., 2006; Rimondini et al., 2002; Roehrs et al., 1984) on measures of ethanol consumption. However, the reinforcing effects of the BZ in isolation were only assessed in the study of Winger et al. (2007), so the other reports were unable to

compare the relative reinforcing effects of the mixture to that of each of its components (i.e., both the BZ and ethanol). Winger et al. (2007) compared the reinforcing effectiveness of intravenous injections of ethanol and flunitrazepam, both alone and as mixtures, in rhesus monkeys and found that the ethanol and flunitrazepam mixture was greater in reinforcing effect than ethanol alone but less than flunitrazepam alone. These results suggest that there would be no advantage to co-administering BZs and ethanol, at least in terms of reinforcing effectiveness, as the mixture would have a lower reinforcing effect than the BZ alone. However, it is unknown if the reinforcing effectiveness of ethanol and BZ mixtures is dependent upon route of administration, which may be critical, as human reports indicate that concurrent BZ and ethanol misuse most often occurs orally (Calhoun et al., 1996; Gahlinger, 2004; Rickert et al., 1999).

The current study extended these findings by using an operant self-administration procedure to compare the reinforcing effectiveness of midazolam, ethanol, and the drugs in combination. To facilitate reliable consumption of all drug mixtures, we elected to combine the solutions with 10% sucrose. This decision was informed, in part, by previous reports of BZs functioning as weak reinforcers in rats (Colins et al., 1984; Finlay et al., 1989; Naruse and Asami, 1987; Oittinen et al., 2000; Pilotto et al 1984; Szostak et al., 1987, but see Falk and Tang, 1985). In addition, stable self-administration of pharmacologically-relevant doses of ethanol typically requires a gradual fading of sucrose (e.g., Samson, 1986; Tolliver et al., 1988), and it is unknown if the addition of a BZ would further impair the rate of acquisition. By combining all solutions with sucrose, we expected higher rates of responding and consumption for all solutions at low response requirements, exposing the animals relatively high doses of the drugs. To compare the relative reinforcing effectiveness, the sensitivity of consumption to increases in cost (i.e., response requirement) was quantified using a behavioral economic approach (Hursh and Silberberg, 2008). We hypothesized that a greater reinforcing effect of a drug condition would “emerge” from sucrose at higher response requirements, given the solution had adequate reinforcing effect. Therefore, if midazolam increases the reinforcing effectiveness of an ethanol-containing sucrose or vice versa, one would expect consumption of the sucrose, midazolam, and ethanol mixture to be less sensitive to increases in response requirement than any of the constituent solutions.

Method

Subjects

Eight male Sprague-Dawley rats were used as subjects. Rats were 12 weeks of age at the onset of the experiment, and initial weights ranged from 347 to 406 g. Rats were pair-housed throughout the experiments. Housing and testing were conducted in a temperature-controlled vivarium (23 °C) with a 12-h light/dark cycle (lights on at 0800 h). Behavioral testing occurred during the light phase, five days per week. Rats were given free access to standard chow and water in their home cage, but not during the 1h experimental sessions. All procedures were conducted in compliance with the National Research Council's Guide for Care and Use of Laboratory Animals (2011) and approved by the University of Mississippi Medical Center's Institutional Animal Care and Use Committee.

Apparatus

Eight custom operant chambers (Gerbrands Corporation; 19 cm h × 23.5 cm w × 22 cm l) equipped with two non-retractable levers (Gerbrands Corporation) were used throughout the study. A single white stimulus light was mounted above each lever. Additionally, a jeweled stimulus light was mounted between the two white stimulus lights. Drug solutions were delivered from 30 ml plastic syringes that were seated in infusion pumps (Razel Scientific, St. Albans, VT, USA) located outside the operant chamber. The solution traveled through polyethylene tubing and was deposited into a stainless steel trough located below the lever. A Macintosh computer equipped with custom interface and software (Mac State) controlled all events in the experimental session and recorded data.

Procedure

Each rat completed a full behavioral economic demand curve function for each drug and drug-combination condition, in a counterbalanced order. The conditions, which were all delivered as solutions mixed in water, consisted of 10% sucrose (S), 10% sucrose + 0.1 mg/ml midazolam (SM), 10% sucrose + 5% w/v ethanol (SE), and 10% sucrose + 0.1 mg/ml midazolam + 5% w/v ethanol (SME). The concentration of midazolam (i.e., 0.1 mg/ml) was based upon the findings of Falk and Tang (1985), wherein a 0.05 mg/ml midazolam and water solution was readily consumed in a schedule-induced polydipsia preparation. Additionally, when mixed with 10% sucrose, self-administration of a 0.1 mg/ml midazolam solution often approaches 3 mg/kg when the response requirement is low (unpublished observations), which corresponds to a dose previously reported to be behaviorally-active when delivered non-contingently (i.e., impairs performance of a force-discrimination task; Bowen et al., 2000). As for the available concentration of ethanol, we have found that Sprague-Dawley rats will reliably self-administer ethanol doses of over 1 g/kg when made available as a 10% sucrose + 5% w/v ethanol solution (unpublished observations). For reference, 0.5 g/kg of orally consumed ethanol has been shown to correlate with blood ethanol levels above 100 mg/dl in rats (Grant and Samson, 1985), which exceeds the National Institute on Alcohol Abuse and Alcoholism (NIAAA) definition of a binge drinking episode in humans (NIAAA, 2004; 80 mg/dl).

Animals were trained during a single one-hour session wherein the active lever was “baited” with food pellets taped to the lever. The solution available during training was part of the counterbalancing. Thus, each solution served as the training stimulus for a subset of animals. Initiation of the session was signaled by illumination of the stimulus light above the active lever. During this training session, presses on the active lever were under a fixed-ratio 1 (FR1) schedule of reinforcement and resulted in delivery of 0.1 ml of the animal’s first counterbalanced condition (i.e., S, SM, SE, or SME) in conjunction with 4 blinks of the jeweled stimulus light, all occurring within a 1-s duration. Presses on the inactive lever were recorded but had no programmed consequences. The positions of the active and inactive levers were counterbalanced across subjects. Upon the completion of each session, fluid receptacles were examined for evidence of unconsumed fluid before being cleaned with a 70% ethanol solution. Unconsumed fluid was not observed after any session during the course of the experiment.

On the sessions following training, an identical program was used, but lever baiting was discontinued. The initial response requirement for 0.1-ml solution deliveries was FR1, which was in effect until stable consumption was observed. Stability was defined as three consecutive sessions wherein the number of earned reinforcers was within 20% of the 3-session mean with no upward or downward trends. The response requirement was subsequently increased in quarter-logarithmic increments (i.e., 1, 3, 6, 10, 18, 32, 56, 100), with each animal meeting stability criteria for each response requirement. This progression continued until the subject earned zero reinforcers for two consecutive sessions (i.e., breakpoint; Hodos, 1961). After an animal completed a full demand function for a condition, the next condition was introduced on the following session. Testing occurred 5 days per week and until each animal reached breakpoint for each solution.

Drugs

Midazolam HCl (West-Ward, Eatontown, NJ) was obtained as a 5 mg/ml solution, with a vehicle of 0.8% sodium chloride, 0.01% edetate disodium, and 1% benzyl alcohol. Ethyl alcohol (95%; Ultra Pure, Darien, CT) was purchased from the University of Mississippi Medical Center pharmacy. All solutions were prepared fresh weekly by combining deionized water with granulated sucrose, midazolam, and/or ethanol.

Data Analysis

For each solution, reinforcing effectiveness was determined using the exponential model of demand, which quantifies the sensitivity of reinforcer consumption to increases in price (Hursh and Silberberg, 2008). The average of three stable days of consumption at a given response requirement was used to represent individual consumption, and the FR response requirement was used to represent price. A custom-designed GraphPad Prism 5.0 template (freely available from the Institutes for Behavior Resources, www.ibrinc.org) plotted reinforcers earned as a function of FR value and the data were fit with the Exponential Model of Demand introduced by Hursh and Silberberg (2008). Specifically, when an individual demand function was analyzed, we elected to exclude the zero from analysis, leaving the mean number of reinforcers earned at the previous response requirement to serve as the final empirically-determined point along the demand function. When calculating aggregate demand functions, an individual animal's zero would be used in the analysis if it could be averaged with another animal's non-zero number of reinforcers for the given response requirement. However, if all animals earned zero reinforcers at a given response requirement, the zero would be excluded from analysis. When analyzing individual demand functions, the scaling variable k was fixed to a shared value of 2.37, as this corresponded to the log 10 value of the greatest mean number of reinforcers earned by any individual animal at any response requirement. Similarly, k was fixed to 2.23 when analyzing aggregate demand functions, as this number corresponded to the greatest mean number of reinforcers earned from the aggregate functions.

Baseline consumption (i.e., stable FR1 consumption) and demand elasticity (α) were each dependent measures of interest with available solution (i.e., S, SM, SE, SME) serving as the independent variable. Hursh and colleagues have argued that reinforcing effectiveness has an inverse relationship to α (Hursh, 2014; Hursh and Roma, 2013; 2016; Hursh and Silberberg,

2008). However, this inverse relationship is somewhat counterintuitive, with smaller α values corresponding to a greater reinforcing effect. To increase clarity, α values were transformed and represented graphically as “Essential Value” such that a greater value reflects a greater reinforcing effect (cf. Roma et al., 2016). The formula for this transformation was introduced by Hursh (2014) and is given in Eq. (1):

$$\text{Essential Value} = 1 \div (\alpha \times (k^{1.5}) \times 100) \quad (1)$$

Additional behavioral economic demand metrics (i.e., $P_{\max}$, $O_{\max}$) were also calculated using a freely available Excel-based demand metrics calculator tool (Kaplan and Reed, 2014). $P_{\max}$ is the price at which demand shifts from inelastic to elastic (e.g., where a 1% increase in price yields a >1% decrease in consumption), and $O_{\max}$ is the output at $P_{\max}$, representing peak expenditure for the commodity. Breakpoint (i.e., BP) was defined as the first response requirement at which an animal failed to earn a reinforcer (Hodos, 1961).

The group mean values for baseline intake (i.e., stable FR 1 consumption) were compared between solutions using repeated measures one-way ANOVA tests with a repeated-measures factor of solution. Demand elasticity (α) values of aggregate demand curves were compared using the Extra Sum-of-Squares F test. The α values of SM, SE, and SME were each individually compared to S (control solution), and p values were corrected using the Benjamini-Hochberg False Discovery Rate Step-Up Procedure (Benjamini & Hochberg, 1995). $P_{\max}$, $O_{\max}$, and BP were determined for each subject and compared between solutions using repeated-measures one-way analysis of variance (ANOVA) tests with a repeated-measures factor of solution (i.e., S, SM, SE, and SME).

Estimations of midazolam and ethanol intake under baseline conditions (mg/kg and g/kg, respectively) were calculated for each animal by first multiplying the number of earned reinforcers by the dose of either midazolam or ethanol; these values were then divided by the weight (kg) of the animal. Statistical significance for all tests was set at $p = 0.05$. Unless otherwise noted, all data are presented as mean $\pm$ SEM.

Results

At the lowest response requirement (i.e., FR1), the number of earned reinforcers was similar across solutions ($F[2.12, 14.83] = 2.26$, *NS*) (Figure 1A). This rate of consumption was sufficient to achieve an average midazolam intake of 4.21 (SD = 1.26) and 3.04 (SD = 1.31) mg/kg when SM and SME were made available, respectively. Mean ethanol consumption was 1.6 (SD = 0.5) and 1.5 (SD = 0.7) g/kg when SE and SME were made available, respectively. Furthermore, intake of midazolam and ethanol decreased as response requirement increased (Table 1).

The Exponential Model provided a good fit to the aggregated data (R^2 values were 0.98 for S, 0.97 for SM, 0.85 for SE, and 0.98 for SME) (Figure 1B). Direct comparison of aggregate α values indicated demand elasticity was different between solutions ($F[3, 16] = 4.0$, $p < 0.05$). Post-hoc analyses revealed that demand elasticity of SM was significantly different

than that of S ($F[1,8] = 19, p < 0.01$), indicating that the midazolam only-containing solution had a greater reinforcing effectiveness relative to sucrose alone. In contrast, demand elasticities of SE and SME were not different from that of S: S vs SE ($F[1,7] = 0.22, NS$), S vs SME ($F[1,7] = 0.008, NS$). These data are represented by histograms of mean Essential Values (derived from α values) in Figure 1C. The additional demand metrics of $P_{\max}$, $O_{\max}$, and BP were found to be similar across solutions: $P_{\max}$: ($F[1.59, 11.16] = 1.72, NS$) (Figure 2A); $O_{\max}$: ($F[3, 28] = 2.28, p = 0.1$) (Figure 2B); BP_0 : ($F[2.153, 15.07] = 0.29, NS$) (Figure 2C). Individual data, including fit of the exponential equation (R^2), Essential Value, $P_{\max}$, $O_{\max}$, and breakpoint across solutions, are shown in Table 2.

Discussion

Rats orally self-administered sucrose solutions that were combined with midazolam and/or ethanol. Under baseline conditions, intake of midazolam- and ethanol-containing solutions was sufficient to achieve what have previously been shown to be behaviorally-active doses (cf. Bowen et al., 2000; Grant and Samson, 1985), suggesting that the animals were exposed to pharmacologically relevant doses, at least at the FR1 response requirement. However, as the response requirement increased, consumption of all solutions declined, corresponding to increasingly lower self-administered doses of the drug-containing solutions (Table 1). The rate at which consumption decreased was similar across solutions, with the exception of the midazolam-containing solution, which was less elastic than sucrose alone. These findings do not support the hypothesis that BZ and ethanol co-administration is maintained by a greater reinforcing effect of the combination relative to either drug in isolation. In fact, given the midazolam-containing solution was the only solution to have a greater reinforcing efficacy than sucrose, these data suggest that the addition of ethanol decreased the reinforcing effectiveness of the midazolam-containing sucrose solution in this preparation. However, it is currently unknown if the generality of these data would be impacted by the examination of higher or lower relative magnitudes of midazolam and/or ethanol.

As described in the introduction, preclinical investigations have reported both increases and decreases in measures of ethanol self-administration following BZ exposure. One explanation for these mixed findings could be that BZs increase the potency of ethanol to produce reinforcing effects, as a leftward shift of an “inverted-U” dose-response function for ethanol could encompass both increases and decreases in ethanol intake. Previous drug-discrimination work has shown that BZs increase the potency of the discriminative stimulus effects of ethanol and vice versa (e.g., Bienkowski and Kostowski, 1998; Jarbe and McMillan, 1983; Schechter, 1998, but see Schechter and Lovano, 1985), which may be predictive of the effect of the combination on reinforcing potency. A topic less frequently examined is the effect of BZs on the reinforcing effectiveness of ethanol, which requires the use of schedules of reinforcement capable of separating reinforcing effectiveness from potency (e.g., progressive-ratio schedule of reinforcement or behavioral economic demand designs). A strength of the current approach (i.e., comparison of elasticity derived from demand curves) is that it enables a comparison of the reinforcing effectiveness of single doses of multiple reinforcers, independent of differences in potency of single drugs (Hursh and Silberberg, 2008; Hursh and Winger, 1995). However, the extent to which behavioral economic analyses are sensitive to the relative proportion of multiple drugs delivered as a

mixture (e.g., unit dose of midazolam relative to ethanol in the current report) has not been formally examined and merits further investigation. Nevertheless, the behavioral economic procedure used in the current study may allow for a better understanding of the seemingly-mixed findings of the effects of BZs on ethanol consumption. The findings of both Winger et al. (2007) and the current study converge to suggest that the reinforcing effectiveness of a BZ and ethanol mixture is not greater than that of the BZ component of the mixture. However, further work is needed to determine if BZ and ethanol co-abuse is truly unattributable to an enhanced reinforcing effectiveness of the combination.

One limitation of the current approach is that we were not able to compare the direct reinforcing effects of midazolam or ethanol because all solutions contained another reinforcer, sucrose. We hypothesized that the addition of sucrose would maintain high levels of intake under baseline conditions, and that solutions with sufficiently-high reinforcing effectiveness would maintain increased responding at higher prices than sucrose alone. Indeed, baseline responding on all solutions was similarly high, and responding for the midazolam only-containing solution (i.e., SM) was defended at higher response requirements than sucrose alone, demonstrating a greater reinforcing effectiveness of this mixture. In contrast, the reinforcing effectiveness of the sucrose and ethanol mixture (i.e., SE) did not differ from that of sucrose, indicating that the dose of ethanol used in the current study did not enhance the reinforcing effects of sucrose. This result was somewhat unexpected, as this concentration of ethanol and sucrose has previously been shown to be less elastic than sucrose alone (Petry and Heyman, 1995), although the schedule of reinforcement and strain of rat differed between the studies. Future studies could better characterize the relative reinforcing effects of midazolam and ethanol within a behavioral economic framework by attempting to decrease or remove the sucrose from the solution. In addition, if both midazolam and ethanol were made available individually, one could assess whether the presence of one of the substances interacts with the reinforcing effectiveness of the other (i.e., cross-price elasticity; see Murphy et al., 2016; Petry and Heyman, 1995), which could provide further insights into the co-abuse of these substances.

Despite the null findings of the current report, the prevalence of BZ and ethanol emergency department visits and fatalities continues to increase (Day, 2014), and determinants of this potentially lethal form of polydrug use remain unclear. Given the abuse liability of BZ and ethanol as individual reinforcers, it seems reasonable to assume that a major determinant of co-administration of these two drugs is related to their reinforcing effects. However, the equivocal findings of the aforementioned investigations of this topic (i.e., Barrett and Weinberg, 1975; Chan et al 1983a,b; Petry, 1995, 1997; Roehrs et al., 1984; Samson and Grant, 1985; Sawyer et al., 2014; Soderpalm and Hansen, 1998; Winger et al., 2007; current report) suggest that there may be little, if any, reliable enhancement of reinforcing effects when co-administering these drugs. One possibility is that BZ and ethanol co-administration is partially attributable to misuse of the medication, as opposed to recreational abuse. For example, an individual may receive a prescription for a BZ and continue to consume large quantities of alcohol as they did before taking the medication, which could lead to severe side effects (e.g., Dorian et al., 1985; Hu et al., 1987; Linnoila et al., 1990; Maickel and Nash, 1986). If these BZ and ethanol overdoses are attributable to patients' ignorance of the negative consequences associated with their co-administration, healthcare providers should

increase efforts to educate BZ prescription recipients of the risks associated with this behavior. Additionally, studies characterizing the behavioral topography of the co-administration of benzodiazepines and ethanol would provide useful information for the management of this increasingly-prevalent health concern.

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Figure 1.

Summary of oral self-administration of sucrose (open symbols), sucrose + midazolam (dark grey symbols), sucrose + ethanol (light grey symbols), and sucrose + midazolam + ethanol (black symbols). (A) Mean $\pm$ SEM baseline consumption (i.e., FR1) across solutions. (B) Aggregated Essential Value across solutions. (C) Aggregated mean demand curves. * $p < 0.05$.

Figure 2.

Additional behavioral economic metrics for sucrose (open symbols), sucrose + midazolam (dark grey symbols), sucrose + ethanol (light grey symbols), and sucrose + midazolam + ethanol (black symbols). (A) Mean $\pm$ SEM $P_{\max}$ across solutions. (B) Mean $\pm$ SEM $O_{\max}$ across solutions. (C) Mean $\pm$ SEM BP₀ (i.e., breakpoint) across solutions.

Table 1

Mean intake of midazolam (MZ) and ethanol (EtOH) across response requirements. Note that only a subset of animals is included at the higher response requirements, reflecting differences in breakpoint between subjects.

	SM		SE		SME		
	MZ mg/kg (SD)	N	EtOH mg/kg (SD)	N	MZ mg/kg (SD)	N	EtOH mg/kg (SD)
<i>Price</i>							
1	4.2 (1.3)	8	1.6(0.5)	8	3.0(1.3)	8	1.5 (0.7)
3	2.9(1.7)	8	0.8 (0.4)	8	1.6(1.0)	8	0.8 (0.5)
6	2.2(1.9)	8	0.8 (0.4)	7	1.0 (0.7)	8	0.5 (0.4)
10	1.5(1.0)	7	0.7(0.3)	6	0.6 (0.6)	7	0.3 (0.3)
18	1.3 (0.8)	3	0.3(0.1)	5	0.7 (0.2)	3	0.4(0.1)
32	0.3 (NA)	1	0.1 (NA)	1	0.2 (NA)	1	0.1 (NA)
56	0.1 (NA)	1					

Table 2

Individual subject data (subjects 1-8) for the goodness of fit of the exponential equation (R^2), Essential Value, P_{max} , O_{max} , and breakpoint across solutions.

	Subject							
	<i>I</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
S								
Fit (R^2)	0.90	0.88	0.89	0.98	0.96	0.97	0.99	0.93
Essential Value	11.7	5.6	5.8	16.8	7.3	13.4	6.7	12.2
PMAX	3.4	5.5	2.1	5.6	2.8	6.3	1.6	5.8
OMAX	321.3	154.0	160.6	461.9	199.7	369.5	184.7	335.9
Breakpoint	18	10	32	32	32	32	10	18
SM	<i>I</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
Fit (R^2)	0.95	0.93	0.69	0.97	0.91	0.97	0.71	0.43
Essential Value	22.4	5.2	39.6	40.1	5.8	5.7	37.4	13.4
PMAX	5.5	3.1	17.7	9.0	2.3	1.5	20.0	8.1
OMAX	615.8	142.1	1086.7	1102.9	160.6	157.2	1026.4	369.5
Breakpoint	32	10	18	100	18	18	32	32
SE	<i>I</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
Fit (R^2)	0.97	0.86	0.91	0.98	1.00	0.88	0.82	0.99
Essential Value	6.4	1.7	19.2	20.7	4.0	17.9	17.9	19.2
PMAX	4.4	1.1	11.3	9.5	1.4	10.2	12.2	9.1
OMAX	175.9	46.2	527.8	568.4	110.3	492.7	492.7	527.8
Breakpoint	18	10	32	32	6	56	32	32
SME	<i>I</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
Fit (R^2)	0.96	0.91	0.98	0.92	1.00	0.95	0.90	0.92
Essential Value	19.2	10.0	6.3	22.4	4.2	2.4	1.8	14.9
PMAX	10.2	5.0	4.3	10.5	2.1	1.4	1.5	7.7
OMAX	527.8	273.7	171.9	615.8	115.5	67.2	49.3	410.5
Breakpoint	56	10	18	32	18	18	18	32